g) Alkyl(meth)acrylat-Polymeren und -Copolymeren mit einem zahlenmittleren Molekulargewicht von etwa 100 000 bis 1 000 000, insbesondere Ethylacrylat/Methylmethacrylat-Copolymeren und Methylacrylat/Ethylacrylat-Copolymeren;

h) Polyvinylacetat mit einem zahlenmittleren Molekulargewicht von etwa 250 000 bis 700 000, ggf. stabilisiert mit Polyvinylpyrrolidon.

12. Futtermittelzusatz nach Anspruch 11, gekennzeichnet durch eine mittlere Korngröße von etwa 0,4 bis 2 mm aufweisen.

13. Futtermittelzusatz nach Anspruch 11 oder 12, dadurch gekennzeichnet, dass er wenigstens ein Enzym enthält, das ausgewählt ist unter Oxidoreduktasen, Transferasen, Lyasen, Isomerasen, Ligasen, Phosphatasen und Hydrolasen.

14. Futtermittelzusatz nach Anspruch 13, dadurch gekennzeichnet, dass die Hydrolase ein Nichtstärkepolysaccharid-spaltendes Enzym ist.

15. Futtermittelzusatz nach Anspruch 14, dadurch gekennzeichnet, dass die Phosphatase Phytase ist.

16. Futtermittelzusatz nach Anspruch 15, dadurch gekennzeichnet, dass er $1*10^3$ bis $1*10^5$ U Phytase pro Gramm Gesamtgewicht umfasst.

17. Pelletierte Futtermittelzusammensetzung, welche neben üblichen Bestandteilen wenigstens einen Futtermittelzusatz nach einem der Ansprüche 11 bis 16 als Beimischung enthält.

18. Verwendung eines Futtermittelzusatzes nach einem der Ansprüche 11 bis 16 zur Herstellung von pelletierten Futtermittelzusammensetzungen.

1/2

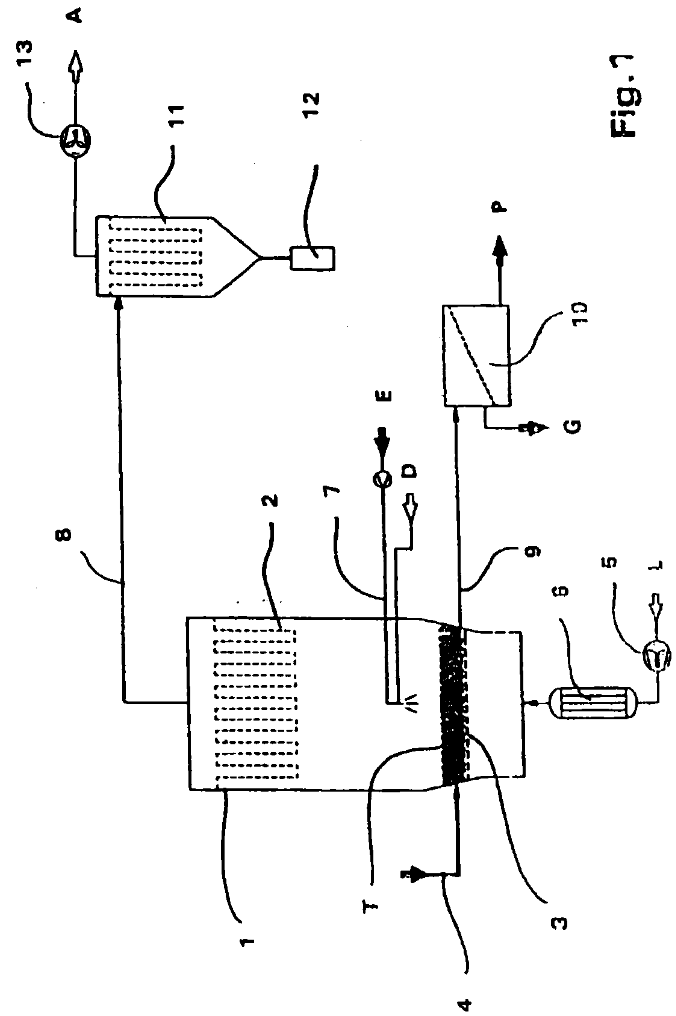

Fig.1

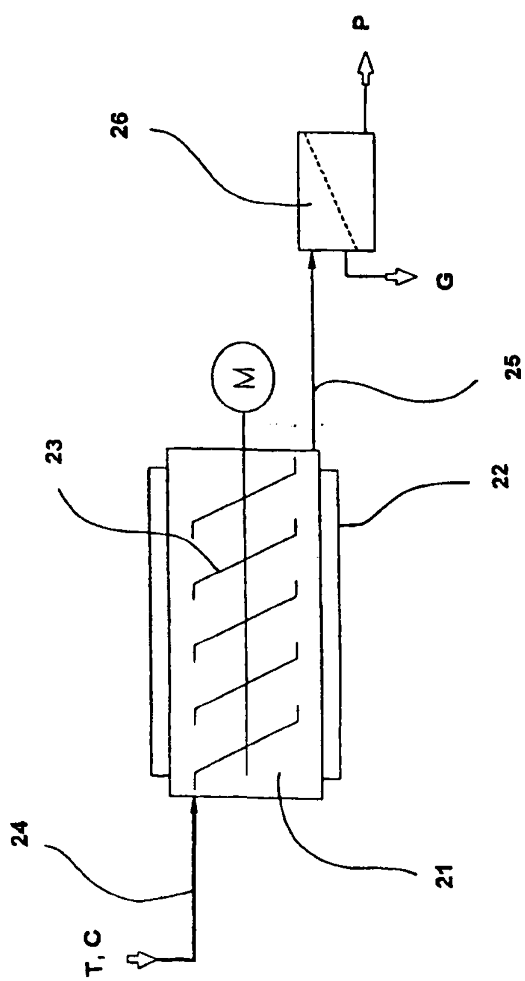

Fig.2

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/05793

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A23K1/00 A23K1/165

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A23K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, CAB Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 00 47060 A (DSM NV ;ANDELA CARL SIDONIUS MARIA (NL); KLEIN HOLKENBORG AUGUSTIN) 17 August 2000 (2000-08-17) examples 4-8 claims 1-4,12-25	1-7, 11-18
E	WO 00 36927 A (BASF AG ;BETZ ROLAND (DE); HARZ HANS PETER (DE); HEINZL WOLFGANG () 29 June 2000 (2000-06-29) page 2, line 38 - line 47 page 3, line 8 - line 15 page 3, line 33 - line 36 page 4, line 1 - line 6 page 4, line 40 -page 5, line 27 page 6, line 1 -page 7, line 32 claims 1-8	1,10-18

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[X] Further documents are listed in the continuation of box C.

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International Application No
PCT/EP 00/05793

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 99 51210 A (GENENCOR INT) 14 October 1999 (1999-10-14) page 4, line 37 -page 5, line 2 page 5, line 13 - line 15 page 6, line 31 - line 33 examples 1-4 claims 1-7,20,21	1,6,7, 11,13
X	WO 98 54980 A (HARZ HANS PETER ;BARENDSE RUDOLF CAROLUS MARIA (NL); GIST BROCADES) 10 December 1998 (1998-12-10) page 11, line 5 - line 17 page 12, line 14 -page 14, line 26 examples 6,7,9 claims 1-5,8,9,12-27	1-7, 11-18
X	WO 97 12958 A (GENENCOR INT) 10 April 1997 (1997-04-10) page 3, last paragraph -page 4, paragraph 1 page 5, paragraph 3 - paragraph 4 examples 1-10 claims 1-7	1,2,4-6, 11-13
Y		7-9
Y	DATABASE WPI Section Ch, Week 199627 Derwent Publications Ltd., London, GB; Class A11, AN 1996-263781 XP002152846 -& JP 08 109126 A (AMANO PHARM KK), 30 April 1996 (1996-04-30) abstract	7,8
Y	WO 94 26883 A (DILLISSEN MARC ;FEIJEN JAN (NL); ANDELA CARL SIDONIUS MARIA (NL);) 24 November 1994 (1994-11-24) page 5, line 9 - line 20 claims 1,2,4-13	7,8
Y	DATABASE WPI Section Ch, Week 199503 Derwent Publications Ltd., London, GB; Class B02, AN 1995-019176 XP002152847 -& JP 06 305960 A (TERUMO CORP), 1 November 1994 (1994-11-01) abstract	9
X	EP 0 913 468 A (GIST BROCADES BV) 6 May 1999 (1999-05-06) column 2, line 39 - line 49 examples 1,2	1,6,7,11

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/05793

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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WO 0036927	A	29-06-2000	DE	19859385 A	29-06-2000
WO 9951210	A	14-10-1999	AU	3637599 A	25-10-1999
WO 9854980	A	10-12-1998	AU	8435798 A	21-12-1998
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			US	6120811 A	19-09-2000
JP 8109126	A	30-04-1996	NONE		
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JP 6305960	A	01-11-1994	NONE		
EP 0913468	A	06-05-1999	JP	11113479 A	27-04-1999
			US	6083538 A	04-07-2000

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INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen: PCT/EP 00/05793

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C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
E	WO 00 47060 A (DSM NV ;ANDELA CARL SIDONIUS MARIA (NL); KLEIN HOLKENBORG AUGUSTIN) 17. August 2000 (2000-08-17) Beispiele 4-8 Ansprüche 1-4,12-25 ---	1-7, 11-18
E	WO 00 36927 A (BASF AG ;BETZ ROLAND (DE); HARZ HANS PETER (DE); HEINZL WOLFGANG () 29. Juni 2000 (2000-06-29) Seite 2, Zeile 38 - Zeile 47 Seite 3, Zeile 8 - Zeile 15 Seite 3, Zeile 33 - Zeile 36 Seite 4, Zeile 1 - Zeile 6 Seite 4, Zeile 40 -Seite 5, Zeile 27 Seite 6, Zeile 1 -Seite 7, Zeile 32 Ansprüche 1-8 --- -/--	1,10-18

[X] Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

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INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen: PCT/EP 00/05793

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
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X	WO 97 12958 A (GENENCOR INT) 10. April 1997 (1997-04-10) Seite 3, letzter Absatz -Seite 4, Absatz 1 Seite 5, Absatz 3 - Absatz 4 Beispiele 1-10 Ansprüche 1-7	1,2,4-6, 11-13
Y	---	7-9
Y	DATABASE WPI Section Ch, Week 199627 Derwent Publications Ltd., London, GB; Class A11, AN 1996-263781 XP002152846 -& JP 08 109126 A (AMANO PHARM KK), 30. April 1996 (1996-04-30) Zusammenfassung ---	7,8
Y	WO 94 26883 A (DILLISSEN MARC ;FEIJEN JAN (NL); ANDELA CARL SIDONIUS MARIA (NL);) 24. November 1994 (1994-11-24) Seite 5, Zeile 9 - Zeile 20 Ansprüche 1,2,4-13 ---	7,8
Y	DATABASE WPI Section Ch, Week 199503 Derwent Publications Ltd., London, GB; Class B02, AN 1995-019176 XP002152847 -& JP 06 305960 A (TERUMO CORP), 1. November 1994 (1994-11-01) Zusammenfassung ---	9
X	EP 0 913 468 A (GIST BROCADES BV) 6. Mai 1999 (1999-05-06) Spalte 2, Zeile 39 - Zeile 49 Beispiele 1,2 ---	1,6,7,11

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INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen
PCT/EP 00/05793

Im Recherchenbericht angeführtes Patentdokument		Datum der Veröffentlichung	Mitglied(er) der Patentfamilie		Datum der Veröffentlichung
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			PL	337464 A	14-08-2000
			ZA	9804834 A	04-01-1999
			ZA	9804835 A	04-01-1999
WO 9712958	A	10-04-1997	AU	718010 B	06-04-2000
			AU	7392496 A	28-04-1997
			EP	0862623 A	09-09-1998
			US	6120811 A	19-09-2000
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			AU	6970594 A	12-12-1994
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			CN	1110059 A	11-10-1995
			EP	0675952 A	11-10-1995
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JP 6305960	A	01-11-1994	KEINE		
EP 0913468	A	06-05-1999	JP	11113479 A	27-04-1999
			US	6083538 A	04-07-2000

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60/095,283 4 August 1998 (04.08.98) US

(71)(72) Applicant and Inventor: RON, Eyal, S. [US/US]; 7 Coach Road, Lexington, MA 02420 (US).

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(54) Title: ASPECTED PARTICLES FOR ORAL DELIVERY

(57) Abstract

An oral delivery vehicle includes an aspected particle including a pharmaceutically active component and excipients, wherein the vehicle is formulated and/or constructed and arranged to provide controlled delivery of the pharmaceutically active component. The aspected particle possesses one dimension that is about an order of magnitude smaller than the other two dimensions. The vehicle may further contain a lubricious coating to improve mouth-feel. The vehicle may further contain a coating to provide sustained drug delivery to the particle.

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ASPECTED PARTICLES FOR ORAL DELIVERY

This application claims priority under 37 C.F.R. §119(e) to co-pending application U.S.S.N 60/069,501 filed December 15, 1997, "Oral Delivery Formulations", and to co-pending application U.S.S.N 60/095,283 filed August 4, 1998, entitled "Aspected Microparticles for Oral Delivery", the contents of which are incorporated herein in their entirety.

Field of Invention

This invention relates to controlled-release pharmaceutical compositions in a aspected geometry dosage form for the administration of drugs.

Background of the Invention

Current orally delivered drugs are formulated in either solid (i.e., tablet, capsule or granules) or liquid (i.e., solution, suspension or emulsion) form. Solid dosage forms are conventionally the dosage forms of choice as they are typically more stable, less expensive to manufacture and have achieved general acceptance by consumers. The manufacture of solid dosage forms typically involves the processing of the drug with suitable excipients in order to produce a freely flowing powder. The type of processing and excipients chosen to manufacture the powder can be altered to provide desired effects such as controlled release of the drug. Once processed, the powder can be directly packaged into sachets, compressed into tablets or filled into capsules. Tablets can further be coated in order to improve palatability or provide controlled release of the drug.

The pediatric population and those who experience difficulty in swallowing primarily use liquid dosage forms. Liquid dosage forms are available orally as solutions, suspensions or emulsions. These liquids often contain colorants and flavorings in an attempt to increase palatability and patient acceptance.

Over 35% of the population are unable to adequately ingest either solid or liquid dosage forms due to physical limitations that include difficulty in swallowing due to esophageal dehydration, "mouth breathing", esophageal lesions or consumption

of anticholinergic medications. Geriatric patients also experience difficulty in chewing due to reduced bulk and tone of oral musculature as well as loss of or degradation in the quality of teeth.

In order to overcome this inability to tolerate solid dosage forms, health care providers typically crush solid dosage forms and disperse them in a semi-solid medium (e.g., applesauce, pudding, etc.). However, when tablets or capsules are tampered with the drug release kinetics of the pharmaceutics are altered. This results in dosing times and concentrations that are sub-optimal. Therefore, pharmaceutical manufacturers provide many drugs with the instructions: "DO NOT CRUSH" (*Hospital Pharmacy*, 21(1), 27, 1996)

Fast dissolving tablets are available as an alternative to pill dosage formats. The tablets are retained in the mouth and rapidly dissolve to release the drug. Limitations to this method include restriction to drugs which do not have unacceptably unpleasant or bitter taste and the immediate release of the drug which prevents sustained release.

A further factor in patient drug non-compliance is the aesthetic response of the patient to the dosage format. When the "mouth-feel" of the dose is unpleasant, the patient is less likely to comply with the dosage regimen. The term mouth-feel is related to the type of sensation or touch that a dosage form produces in the mouth upon ingestion and is not concerned with the chemical stimulation of olfactory nerves or taste buds. However for the formulation to be successful, the overall effect in the mouth is important. In general, gritty or gummy textures are undesirable. A smooth texture is preferred. *See,* Pharmaceutical Dosage Forms; Edited by Leiberman, H.A. and Lachman, L. Marcel Dekker, Inc. New York, Volume I, pp. 291.

Currently available are free flowing particulant drug platforms in the form of rounded spheres which are currently marked under the tradenames Spoon Dose™ (Fuisz) and Pharmazome™ (Elan). The powders are added directly to food or drinks by the user just prior to ingestion. While such a drug delivery mechanism may be attractive to those wishing to avoid pills, the particles still retains their sense of grittiness and provides an unacceptable mouth-feel to the user.

In attempts to address some of the above issues, different formulations have been investigated. Formulations of nano- or macrogranulars have been reported in US

5,618,527. In order to prevent the sensation of grittiness US 5,618,527 describes formulations in either liquid or tablet form consisting of spherical particles of not greater then 125 µm in diameter. Additionally, the particles are required to have smooth edges. These requirements severely limit the flexibility of the drug delivery of the drug.

An alternative attempt to reduce the sensation of grittiness by using a blend of a gritty drug product with a seedy fruit, such as strawberries, was described in US 5,102,664. In this combination, the seedy fibrous fruit texture masks the grittiness of the drug.

Flake-like geometries have been used to improve patient compliance in the administration of dosage formats. Peters *et al.* in US 4,581,232 describes the use of a flake-like structure for the microencapsulation of drugs in order to produce a suitable taste-masking effect for bitter after-taste medications. While the flake-format reduced patient aversion to the medication, the flake format yielded rapid bioavailability. Thus, this formulation was an unstable format for controlled drug delivery.

There is a need for controlled-release formulations for pharmaceutical administrations that are easy to ingest; have a time-dependent release that offset the short half-life of the active ingredient and thus minimize multiple dosages; exhibit satisfactory stability; and are sufficiently palatable and convenient to administer and that possess the appropriate mouth feel to ensure patient compliance. These and other limitations of the prior art are met in the present invention.

Summary of the Invention

It is an object of the invention to provide an oral drug delivery platform that is easy to ingest and retain and that does not possess the limitations of prior art solid and liquid form dosages. It is a further object of the invention to provide a drug delivery format that is spoon feedable.

It is a further object of the present invention to provide an alternative drug dosage format to the pill or capsule format.

It is a further object of invention to provide a drug delivery vehicle with enhanced mouth feel for increased patient compliance. It is a further object of the invention to provide a drug delivery vehicle with an acceptable organoleptic-feel.

The term organoleptic-feel is related to the stimulating any of the organs of sensation (PDR Medical Dictionary, Medical Economics, Montvale, NJ, 1995).

It is still a further object of the invention to provide a dosage form that is easy to ingest, and that provides a reservoir for controlled delivery of the drug.

These and other objects of the invention are achieved by the drug delivery platforms of the invention.

The present invention provides an oral delivery platform which overcomes the noncompliance issues in the geriatric and other patient populations and which optimizes the absorption of drugs.

The present invention provides a sustained delivery vehicle. The vehicle includes a pharmaceutically active component and other pharmaceutical acceptable excipients. The vehicle is flat or of an aspected morphology which provides an acceptable mouth feel. By aspected morphology, as that term is used herein, it is meant that at least one dimension of the vehicle is considerably smaller than the scale of the largest dimension. The smallest dimension may be one order of magnitude smaller than the largest dimension and may be up to three orders of magnitude (1000-fold) smaller. The vehicle is formulated and/or constructed and arranged to provide controlled delivery of the pharmaceutically active component to the desired site within the patient.

The aspected particles may be administered to the patient as a free-flowing powder. Alternatively, the aspected particles may be incorporated into a viscous base having a consistency capable of being spoon-fed. The viscous base may be food or non-food, such as by way of example, applesauce or cellulosic gel. The aspected particles optionally may be provided premixed with the base or it may be supplied separately from the base for mixing just prior to consumption. A delivery vehicle comprised of aspected particles including a pharmaceutically active component may be added to or mixed into the viscous base. The vehicle is flat of an aspected morphology which provides an acceptable mouth feel, while the viscous base facilitates swallowing and masks the presence of the drug. The vehicle may be formulated and/or constructed and arranged to instant release or to provide controlled delivery of the pharmaceutically active component to the desired site within the patient.

Use of highly aspected particles as a drug delivery vehicle provides significant benefits in controlling the release kinetics of a drug. Aspected particles provide uniform surfaces for drug diffusion and release over time. In addition, aspected particles experience a much less dramatic change in volume/surface area ratio as the particles dissolve, as compared to spherical particles. Where the volume/surface area ratio remains relatively constant, drug delivery vehicle architecture and design is simplified. Highly aspected particles for use in drug delivery vehicles may incorporate features known to be effective in the controlled release of drugs. For example, the release kinetics of the drug may be controlled by incorporation of hydrophobic or water-insoluble excipients to the aspected particle in order to retard drug dissolution. Similarly, coating the aspected particle with hydrophobic or water-insoluble polymeric films provides controlled drug release. Incorporation of the appropriate excipients into the aspected drug delivery vehicle provides controlled release kinetics

In one embodiment of the invention, the particles are coated to enhance mouth-feel. The particles may be coated with a fast swellable hydrogel, which results in enhanced palatability and mouth feel upon wetting. In another embodiment of the invention, the drug-incorporated aspected particles may be coated with a suitable film-former polymer or hydrogel that eliminates the damage to the epithelial cells of the esophagus additionally to enhancing the mouth-feel.

In one aspect of the invention, the drug delivery vehicle is are provided in a flat morphology. The drug-incorporated aspected particles may be administered in a variety of media, including liquid, tablet and food-feedable bases. The aspected particles are formulated to provide all the benefits for controlling the release kinetics of the drug as described herein.

An additional feature of the invention is that the flat morphology of the particles eliminates or reduces any unpleasant organoleptic sensations. The aspected particles are coated with a gel which forms a waterlike environment surrounding the particle. The mouth does not "see" the particle and no sensory reaction occurs.

The drug delivery vehicle and the spoon-feedable drug delivery vehicle described herein overcome the limitations of the prior art in providing a dosage format that is easy to administer, provides controlled drug release kinetics and

improves patient compliance. An further advantage of the present invention, includes increased ease of manufacturing and processing control. This alleviates of many of the shortcomings of nano- and macro-granules in terms of particle size and manufacturing constraints when dealing with spherical particles.

Brief Description of the Drawing

This invention is described with reference to the Figures, which are presented for the purpose of illustration only and which are in not limiting of the invention and in which:

Figure 1 is a schematic illustration of an aspected particle demonstrating the difference between flat particle dissolution and spherical particle in terms of constant surface/ volume ratio;

Figure 2 is a cross-sectional view of a hydrogel coated aspected particle that swells upon contact with water;

Figure 3 is a schematic illustration of multilayers aspected particles in which 3A illustrates drug layers in center layer "sandwiched" between two layers which do not contain drug but control the mouth-feel and the release rate; and 7B illustrates three different layers which may or may not contain drug.

Figure 4 is a cross-sectional view of an aspected particle having a core containing the pharmaceutically active agent and a film forming coating to control diffusion and release of the drug;

Figure 5 is a schematic illustration of a aspected particulates having a core of swellable hydrogel, drug and an outer membrane in which the swellable hydrogel core assists to push the drug from the aspected particle out in a controlled fashioned through the coating;

Detailed Description of the Invention

The present invention provides a novel oral drug delivery platform. The drug delivery vehicle may be advantageous in the administration of drugs to patients who experience difficulties in swallowing and/or tolerating medication in pills or tablets form. According to the invention, the drug may be incorporated into aspected particles that can be directly administered to the patient or that can be introduced

into foods, aqueous liquids or semi-solid bases to form a spoon-able or drinkable drug delivery system. The aspected particle may be readily administered to a patient to provide rapid or sustained drug delivery without leaving an undesirable organoleptic feel.

It has been observed previously that spherical or granular particulates leave an undesirable mouth-feel. The present invention has recognized that drugs that are incorporated into aspected particles possess enhanced mouth-feel by eliminating or reducing the gritty feel in the mouth. Because the flat morphology has a better mouth feel than current spherical delivery vehicles, e.g., U.S. 5,516,537, it is anticipated that they will be better tolerated by the patient, leading to more complete dosages and higher compliance.

The present invention also recognizes that oral dosage forms containing pharmaceutically active substances that are apportioned into many individual units, here the aspected particle of the invention, are more reliable in their biopharmaceutical behavior. Upon ingestion the particles spread over a large section of the intestinal tract and provide a improved uptake of the released drug. Also, the movement and quantity of the digestive fluids do not noticeably influence multiparticulate dosage forms, owing to the large number of individual particles that compensate for each other. Therefore, bioavailability is more reliable in such multiparticulate form than in monolithic dosage forms.

The aspected particle of the present invention, used as a drug delivery vehicle, includes pharmaceutical active or drug and a synthetic polymer or naturally occurring material which is compatible with the drug. The particle has an aspected pseudo-two dimensional morphology. By aspected morphology, as that term is used herein, it is meant that at least one dimension of the vehicle is considerably smaller than the scale of the largest dimension.

Figure 1 illustrates a highly aspected particle of the invention. An aspected particle 10 is formulated to include a desired pharmaceutic agent. It may further include a base and suitable excipients to provide desired properties, such as stability. The particle 10 is aspected, by which it is meant, that the particle has at least one dimension which is much smaller than the largest dimension of the particle. The smallest dimension may be one order of magnitude smaller than the largest

dimension and may be up to three orders of magnitude (1000-fold) smaller. The thickness of the aspected particle typically is the dimension which is smaller than the width or length. Typically the width to thickness ratio is in the range of 3:1 to about 1000:1. In preferred embodiments, the particle is about 100 nm to about 10 mm along the longest dimension.

The particle may be a substantially flat, thin layer, and thus possesses one dimension that is substantially less than the other two dimensions. The particle may be substantially planar or somewhat curvilinear. It may have an uneven surface, such as breakfast cereal flake. The particles are preferably free flowing and are of relatively uniform and consistent size and morphology.

The particle also includes pharmaceutically acceptable excipients to aid in the preparation of a stable pharmaceutical composition. Excipients include additives which have no therapeutic effect but which provide a desirable attribute to the drug delivery vehicle. Pharmaceutically acceptable excipients are well known and understood by those skilled in the art. Exemplary excipients include antioxidants, fillers, buffers, antibiotics, flavoring, colorants, adhesives, binders and the like. In particular, the pharmaceutically active compound may be incorporated into a natural or synthetic base or filler with which it is compatible. Suitable fillers include cellulosics, poloxamers and polyethyleneglycols.

The aspected nature of the particle according to the invention provides a reduced organo-leptic sensation; however, the particles may be further modified to improve mouth-feel.

In one aspect of the invention, the aspected particle is coated with a lubricious layer. The lubricious layer is slippery to the touch which facilitates the swallowing of the particles. An additional advantage of the hydrogel-coated particle is that the low friction surface reduces damage to the epithelial cells of the esophagus in addition to enhancing mouth-feel. The lubricious coating may be a hydrophobic or hydrophilic coating. Materials suitable for hydrophobic coating includes oils, such as silicone oils or siloxanes, and other low friction materials. Materials suitable for hydrophilic coatings include hydrogel polymer which become hydrated and swell in contact with an aqueous medium. The lubricious layer may contain flavorings and colorants for further enhancement of consumer appeal.

In preferred embodiments, the aspected particles of the invention are coated with an appropriate hydrogel. The hydrogel-coated particle swells upon contact with water to provide a smooth sensation and texture that enhances the mouth-feel and allows as easy as possible swallowing. Figure 2 demonstrates a hydrogel-coated, highly aspected particle **20** of the invention. A flat or aspected particle **10** is formulated, as in Figure 1, to include a desired pharmaceutic agent. The particle **10** may be coated with a gel coating **22**. Upon exposure to moisture, for example, in the mouth or other body cavities, the coating swells to give a lubricious, slippery coating. Exemplary hydrogels include, by way of example only, polyvinylpyrrolidone, polyvinyl alcohols, poly(N-vinyl lactams), polyethylene oxides, polyvinyl ethers, poly(acrylic acids) and derivatives thereof.

The aspected particles may be dispersed in an aqueous carrier substantially immediately prior to administration. The aspected particles are thereby combined with one or more gelling or swelling agents capable of forming a viscous medium around the particles in an aqueous carrier as well as being provided with a masking surface layer when dispersed in the aqueous carrier. This serves to mask uneven surfaces on the aspected particles and prevent them from adhering to oral mucosa when the composition is ingested and thus makes it easier to administer large dosages of an active substance. The masking surface layer is preferably provided by an increased viscosity of the viscous medium in the immediate vicinity of the particles relative to the viscosity of the surrounding aqueous carrier. A ready-to-use composition is prepared by mixing the composition with an aqueous carrier substantially immediately prior to administration of the composition.

In another aspect of the invention, the aspected particle of the invention is formulated to provide a desired kinetics of drug release. The particle may be designed for instantaneous release or for sustained release over periods of hours to days. The particle may be designed for linear (zero or first order), or non-linear drug release kinetics. The aspected morphology provides certain advantages over a spherical particle in drug release kinetics. The release kinetics from a spherically shaped delivery system is highly dependent on the surface area to volume ratio of the sphere. This ratio is highly dependent on the size distribution of the spheres. In contrast, with flat morphology the surface area to volume ratio is essentially

independent of the size. This is demonstrated in Figure 1, which shows the relatively constant surface area for an aspected particle **20** as it dissolves. Surface area changes as a function of the square of the particle dimensions in a pseudo-rectangular or disc-like particle, such as the aspected particle **20**. This is compared to the dramatic change in surface area spherical particle **22**, which is a cubed relationship. The surface area of a sphere changes as a cubic function of the radius. This in turn means more precisely controlled release kinetics. See, Ron and Langer (Chapter 4) and Gupta and Robinson (Chapter 6) in *Treatise on Controlled Drug Delivery Fundamentals, Optimization, Applications;* Edited by Agis Kydonieus, Marcel Dekker, Inc., New York, 1991; for additional information, which is hereby incorporated by reference.

Selection of the appropriate additives or excipients also effects controlled drug delivery. Additionally, the particle may contain inert excipients to control drug stability and dissolution rates. Incorporating hydrophobic and/or water insoluble polymers in the system will impede the rate of water penetration into the system and therefor will slow down the dissolution rate of the drug. Thus, the release rate is controlled, in part, by the relative solubilities of the drug and base excipients. For example, for a water soluble drug, one may choose a water-insoluble base to retard the release rate of the drug. Similarly, for a water-soluble drug one may select a water-insoluble base to retard delivery.

Exemplary excipients for this purpose include polyvinyl alcohol, polyvinylpyrrolidone, methyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, agar, carrageenan, xanthan, polyethylene glycol, a copolymer of acrylic and methacrylic acid esters, ethylcellulose, cellulose acetate, cellulose acetate phthalate, poly(methyl methacrylate), poly(methyl acrylate), polyethylene, polypropylene, poly(ethylene oxide), PET, poly(vinyl isobutyl ether), poly(vinyl acetate), poly(vinyl chloride), polyurethane, pectin, furcellaran, starch, zein, gelatin, collagen, polygeline, alginic acid, propylene glycol alginate or sodium alginate. One embodiment of the invention utilizes a matrix layer of a water soluble or swellable polymers, such as hydroxypropyl cellulose (e.g., 40-95% by weight and having a molecular weight above 100,000) and a homopolymer of ethylene oxide (e.g., 5-60 wt% and having a molecular weight from 3,000,000 to 5,000,000), a

water-insoluble polymer selected from the group consisting of ethyl cellulose, propyl cellulose, polyethylene and polypropylene (0-10wt%) and 2-10% of a plasticizer for controlled drug delivery.

The use of specific polymeric and hydrogel coatings allows engineering of drug products capable of being delivered to a patient in a relatively targeted fashion. In one embodiment, a drug product can be enteric coated so that the drug product will pass through the stomach into the intestine prior to initiation of release. Suitable coatings include ethylcellulose, polyvinylchloride, methylcellulose, polyurethane, cellulose acetate, polycarbonate, polyethylene, polypropylene, shellac and polymers of acrylic and methacrylic acids and esters of it.

The particle may be coated with one or more coatings, and the coatings may be the same or different, all to obtain the desired release kinetics. Interested readers are directed to the Hand Book of Pharmaceutical (2nd Edition., A. Wade & P.J. Welker, Eds., American Pharmaceutical Assoc., Washington, D.C. 1994) for further detail, which is hereby incorporated by reference. Alternatively, the particle can be designed to give a predetermined sustained release profile (i.e., zero or first order release kinetics) from moment of ingestion. The appropriate materials for use as the delivery vehicle will be readily apparent to one skilled in the art.

The aspected particles of the invention may be incorporated into a bolus system (e.g., a sugar tablet permeated with the active to be delivered), which is formulated for immediate dissolution and release in the mouth. Such systems are used in place of swallowable tablets for those patients that can not tolerate tablets. The disadvantage of this system is that it is not possible to achieve sustained delivery. However, the aspected particle of the present invention which has been formulated for sustained drug delivery may be incorporated into a bolus system to achieve controlled drug release. Thus, the sugar tablet is taken into the mouth by the patient where it dissolves, releasing the aspected drug-incorporated aspected particles of the invention. The aspected particles are then swallowed by the patient. The particles are non-gritty and have an acceptable mouth feel so that the patient can swallow them without a gagging reflex or unpleasant feeling in the mouth.

In other preferred embodiments, hydrogel coatings may be used to provide a controlled release of the drug. Hydrogel coatings may be used to coat the outer

surface of the aspected particle. Thus, the gel provides a physical barrier to diffusion of the drug, which slowly swells with water from the physiological environment. The water swollen coating permits drug diffusion. Where it is desired that the release rate be relatively slower, the hydrogel may be selected to be slow swelling. Conversely, where it is desired that the release rate be relatively faster, the hydrogel may be selected to be rapidly swelling. In yet another embodiment of the invention, the particle is coated with a rapidly swelling hydrogel. The rapid swelling and volume change of the coating is effective to disintegrate the particle, thereby providing substantially immediate drug delivery. Hydrogels having the above-noted swelling properties are well-know in the art.

These hydrogel coatings may be the same or different from those used as lubricious coatings described hereinabove. Thus, in one embodiment of the invention a single hydrogel layer is included which provides both a diffusion barrier for controlled drug delivery and a lubricious coating for improved mouth feel. In other embodiments of the invention, an inner coating is applied to control drug diffusion and an outer coating is used as the lubricious coating.

In other embodiments, a porosigen may be included in the coating, which is water-soluble and which dissolves in water to generate pores in the membrane to permit the release of the drug from the core in an aqueous environment. The porosigen may be selected from the group consisting of polyvinyl alcohol, polyvinylpyrrolidone, polyethyleneglycol, lactose, fumaric acid, citric acid, tartaric acid, sodium citrate, sodium bicarbonate, sodium fumarate, sodium carbonate, monosaccharides and disaccharides, hydroxypropylmethylcellulose, microcrystaline cellulose, polymers of acrylic and methacrylic acids, esters of polyurethane or polyvinylchloride, and potassium or sodium chlodires.

In other embodiments, an additive may be included in the coating which is enzymatically degradable and will degrade to generate pores in the membrane to permit the release of the drug from the core in the appropriate site at the gastrointestinal tract. The additive may be selected from compounds containing azo bonds, which will degrade in the lower gastrointestinal tract, (e.g., colon) in the presence of azo-reductase. Therefore the release will initiate only at the colon. For example, pectin is a suitable compound.

In another aspect of the invention, the drug is incorporated into the particle as a solid dispersion. The solid dispersion may also include acid or base components in order to control the pH for optimal drug dissolution rates. Exemplary acid components include adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid and tartaric acid, and base components include calcium carbonate, calcium hydroxide, magnesium hydroxide, sodium bicarbonate, sodium carbonate, sodium citrate and sodium hydroxide. The solid dispersion may include a surfactant component selected from sodium lauryl sulphate, a sodium carboxylate, an alkyl sulphate, a polyethylene glycol ester, a polyethylene ether, an ethoxylated sorbitan ester and an alkyl trimethylammonium halide and mixes.

A drug product formulated in this manner has the following advantages: it is easy to ingest; as it is likely to stick into interstitial cavities of the mouth and as a result will not leave a residual sensation as spherical-shaped products do; it is relatively uniform in flow and handling characteristics for consumer appeal and ease of manufacturing; it possesses a controllable surface area to volume ratio to provide reproducible dissolution/release property compared with spherically shaped particles; it provides a controlled release kinetics that offset the short half-life of the active ingredient and thus does not require multiple dosages; it exhibits satisfactory stability; and it is sufficiently palatable and convenient, and has and acceptable mouth feel so as to ensure greater patient compliance over other current spherical-shaped products.

In another aspect of the invention, the particle may be incorporated into a semi-solid base to form a spoon-able drug delivery system. The semi-solid base may be comprised of pectin, guar gum, xanthan gum, gum arabic, gum acacia, locust bean gum, carageenan gum, alginic acid, psyllium hydrocolloid, oat bran gum, rice bran gum, glucomannan, tragacanth gum, karaya gum, tapioca, corn starch, cellulose gums, agar, gelatin, polyacrylates, polysaccharides, polyvinylpyrrolidone, pyrrolidones, polyols, collagen, polyethylene glycols, polyvinyl alcohols, polyethers, polyesters, natural or synthetic oils, liquid paraffin, beeswax, silicon waxes, natural or modified fatty acids, or combinations of thereof. Additionally viscous fruit purees such as apple, prune, apricot, pear, pineapple, banana, grape, strawberry, raspberry, blackberry, boysenberry, loganberry, dewberry, gooseberry, cranberry, mulberry,

elderberry, blueberry, fig, currant, kiwi may be used.

The invention may be applied to populations which experience difficulties in taking conventional solid and liquid dosage formats. For example, geriatric, pediatric, oncology patients or other patients who cannot swallow will benefit from a spoonable drug delivery dosage form. Similarly to the elderly, young children who cannot handle the swallowing of a tablet prefer a dosage form that could be spoon-fed to them. Cancer patients who undergo radiation therapy of the head and neck area or take chemotherapeutic drugs experience the lack of formation of saliva and/or esophagatits, which result in inability to take solid food such as tablets.

The active compounds that may be loaded into the drug delivery platforms of the present invention are any substances having biological activity, including proteins, polypeptides, polynucleotides, nucleoproteins, polysaccharides, glycoproteins, lipoproteins, and synthetic and biologically engineered analogs thereof.

Examples of biologically active compounds that might be utilized in a delivery application of the invention include literally any hydrophilic or hydrophobic biologically active compound. Preferably, though not necessarily, the drug is one that has already been deemed safe and effective for use by the appropriate governmental agency or body. For example, drugs for human use listed by the FDA under 21 C.F.R. 330.5, 331 through 361; 440-460; drugs for veterinary use listed by the FDA under 21 C.F.R. 500-582, incorporated herein by reference, are all considered acceptable for use in the present invention.

The term "biologically active compound" includes pharmacologically active substances that produce a local or systemic effect in animals, plants, or viruses. The term thus means any substance intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease or in the enhancement of desirable physical or mental development and conditions in an animal, plant, or virus. The term "animal" used herein is taken to mean mammals, such as primates, including humans, sheep, horses, cattle, pigs, dogs, cats, rats, mice; birds; reptiles; fish; insects; arachnids; protists (e.g. protozoa); and prokaryotic bacteria. The term "plant" means higher plants (angiosperms, gymnosperms), fungi, and prokaryotic blue-green "algae" (i.e. cyanobacteria).

The pharmaceutically active compound may be any substance having

biological activity, including proteins, polypeptides, polynucleotides, nucleoproteins, polysaccharides, glycoproteins, lipoproteins, and synthetic and biologically engineered analogs thereof. The term "protein" is art-recognized and for purposes of this invention also encompasses peptides. The proteins or peptides may be any biologically active protein or peptide, naturally occurring or synthetic.

Examples of proteins include antibodies, enzymes, steroids, growth hormone and growth hormone-releasing hormone, gonadotropin-releasing hormone, and its agonist and antagonist analogues, somatostatin and its analogues, gonadotropins such as luteinizing hormone and follicle-stimulating hormone, peptide-T, thyrocalcitonin, parathyroid hormone, glucagon, vasopressin, oxytocin, angiotensin I and II, bradykinin, kallidin, adrenocorticotropic hormone, thyroid stimulating hormone, insulin, glucagon and the numerous analogues and congeners of the foregoing molecules.

Classes of pharmaceutically active compounds include, but are not limited to, anti-AIDS substances, anti-cancer substances, antibiotics, immunosuppressants (e.g. cyclosporine) anti-viral substances, enzyme inhibitors, neurotoxins, opioids, hypnotics, antihistamines, lubricants tranquilizers, anti-convulsants, muscle relaxants and anti-Parkinson substances, anti-spasmodics and muscle contractants, miotics and anti-cholinergics, anti-glaucoma compounds, anti-parasite and/or anti-protozoal compounds, anti-hypertensives, analgesics, anti-pyretics and anti-inflammatory agents such as NSAIDs, local anesthetics, ophthalmics, prostaglandins, anti-depressants, anti-psychotic substances, anti-emetics, imaging agents, specific targeting agents, neurotransmitters, proteins, cell response modifiers, and vaccines.

A more complete listing of classes of compounds suitable for loading into polymers using the present methods may be found in the Pharmazeutische Wirkstoffe (Von Kleemann et al. (eds) Stuttgart/New York, 1987, incorporated herein by reference). Examples of particular pharmaceutically active substances are presented below:

Anti-AIDS substances are substances used to treat or prevent Autoimmune Deficiency Syndrome (AIDS). Examples of such substances include CD4, 3'-azido-3'-deoxythymidine (AZT), 9-(2-hydroxyethoxymethyl)-guanine acyclovir(), phosphonoformic acid, 1-adamantanamine, peptide T, and 2',3' dideoxycytidine.

Anti-cancer substances are substances used to treat or prevent cancer. Examples of such substances include methotrexate, cisplatin, prednisone, hydroxyprogesterone, medroxyprogesterone acetate, megestrol acetate, diethylstilbestrol, testosterone propionate, fluoxymesterone, vinblastine, vincristine, vindesine, daunorubicin, doxorubicin, hydroxyurea, procarbazine, aminoglutethimide, mechlorethamine, cyclophosphamide, melphalan, uracil mustard, chlorambucil, busulfan, carmustine, lomusline, dacarbazine (DTIC: dimethyltriazenomidazolecarboxamide), methotrexate, fluorouracil, 5-fluorouracil, cytarabine, cytosine arabinoxide, mercaptopurine, 6-mercaptopurine, thioguanine.

Antibiotics are art recognized and are substances which inhibit the growth of or kill microorganisms. Antibiotics can be produced synthetically or by microorganisms. Examples of antibiotics include penicillin, tetracycline, chloramphenicol, minocycline, doxycycline, vanomycin, bacitracin, kanamycin, neomycin, gentamycin, erythromicin and cephalosporins.

Anti-viral agents are substances capable of destroying or suppressing the replication of viruses. Examples of anti-viral agents include a-methyl-P-adamantane methylamine, 1,-D-ribofuranosyl-1,2,4-triazole-3 carboxamide, 9-[2-hydroxy-ethoxy]methylguanine, adamantanamine, 5-iodo-2'-deoxyuridine, trifluorothymidine, interferon, and adenine arabinoside.

Enzyme inhibitors are substances which inhibit an enzymatic reaction. Examples of enzyme inhibitors include edrophonium chloride, N-methylphysostigmine, neostigmine bromide, physostignine sulfate, tacrine HCl, tacrine,1-hydroxy maleate, iodotubercidin, p-bromotetramisole, 10-(alpha-diethylaminopropionyl)- phenothiazine hydrochloride, calmidazolium chloride, hemicholinium-3, 3,5-dinitrocatechol, diacylglycerol kinase inhibitor I, diacylglycerol kinase inhibitor II, 3-phenylpropargylamine, N6-monomethyl-L-arginine acetate, carbidopa, 3-hydroxybenzylhydrazine HCl, hydralazine HCl, clorgyline HCl, deprenyl HCl,L(-)-, deprenyl HCl,D(+)-, hydroxylamine HCl, iproniazid phosphate, 6-MeO-tetrahydro-9H-pyrido-indole, nialamide, pargyline HCl, quinacrine HCl, semicarbazide HCl, tranylcypromine HCl, N,N-diethylaminoethyl-2,2-diphenylvalerate hydrochloride, 3-isobutyl-1-methylxanthne, papaverine HCl, indomethacind, 2-cyclooctyl-2-hydroxy-

ethylamine hydrochloride, 2,3-dichloro-a-methylbenzylamine (DCMB), 8,9-dichloro-2,3,4,5-tetrahydro-1H-2-benzazepine hydrochloride, p-aminoglutethimide, p-aminoglutethimide tartrate,R(+)-, p-aminoglutethimide tartrate,S(-)-, 3-iodotyrosine, alpha-methyltyrosine,L-, alpha -methyltyrosine,D L-, acetazolamide, dichlorphenamide, 6-hydroxy-2-benzothiazolesulfonamide, and allopurinol.

Neurotoxins are substances which have a toxic effect on the nervous system, e.g. nerve cells. Neurotoxins include adrenergic neurotoxins, cholinergic neurotoxins, dopaminergic neurotoxins, and other neurotoxins. Examples of adrenergic neurotoxins include N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine hydrochloride. Examples of cholinergic neurotoxins include acetylethylcholine mustard hydrochloride. Examples of dopaminergic neurotoxins include 6-hydroxydopamine HBr, 1-methyl-4-(2-methylphenyl)-1,2,3,6- tetrahydro-pyridine hydrochloride, 1-methyl-4-phenyl-2,3- dihydropyridinium perchlorate, N-methyl-4-phenyl-1,2,5,6- tetrahydropyridine HCl, 1-methyl-4-phenylpyridinium iodide.

Opioids are substances having opiate like effects that are not derived from opium. Opioids include opioid agonists and opioid antagonists. Opioid agonists include codeine sulfate, fentanyl citrate, hydrocodone bitartrate, loperamide HCl, morphine sulfate, noscapine, norcodeine, normorphine, thebaine. Opioid antagonists include nor-binaltorphimine HCl, buprenorphine, chlornaltrexamine 2HCl, funaltrexamione HCl, nalbuphine HCl, nalorphine HCl, naloxone HCl, naloxonazine, naltrexone HCl, and naltrindole HCl.

Hypnotics are substances, which produce a hypnotic effect. Hypnotics include pentobarbital sodium, phenobarbital, secobarbital, thiopental and mixtures, thereof, heterocyclic hypnotics, dioxopiperidines, glutarimides, diethyl isovaleramide, a-bromoisovaleryl urea, urethanes and disulfanes.

Antihistamines are substances, which competitively inhibit the effects of histamines. Examples include pyrilamine, chlorpheniramine, tetrahydrazoline, and the like.

Lubricants are substances that increase the lubricity of the environment into which they are delivered. Examples of biologically active lubricants include water

and saline.

Tranquilizers are substances, which provide a tranquilizing effect. Examples of tranquilizers include chloropromazine, promazine, fluphenzaine, reserpine, deserpidine, and meprobamate.

Anti-convulsants are substances, which have an effect of preventing, reducing, or eliminating convulsions. Examples of such agents include primidone, phenytoin, valproate, Chk and ethosuximide.

Muscle relaxants and anti-Parkinson agents are agents which relax muscles or reduce or eliminate symptoms associated with Parkinson's disease. Examples of such agents include mephenesin, methocarbomal, cyclobenzaprine hydrochloride, trihexylphenidyl hydrochloride, levodopa/carbidopa, and biperiden.

Anti-spasmodics and muscle contractants are substances capable of preventing or relieving muscle spasms or contractions. Examples of such agents include atropine, scopolamine, oxyphenonium, and papaverine.

Miotics and anti-cholinergics are compounds, which cause bronchodilation. Examples include echothiophate, pilocarpine, physostigmine salicylate, diisopropylfluorophosphate, epinephrine, neostigmine, carbachol, methacholine, bethanechol, and the like.

Anti-glaucoma compounds include betaxalol, pilocarpine, timolol, timolol salts, and combinations of timolol, and/or its salts, with pilocarpine.

Anti-parasitic, -protozoal and -fungals include ivermectin, pyrimethamine, trisulfapyrimidine, clindamycin, amphotericin B, nystatin, flucytosine, natamycin, and miconazole.

Anti-hypertensives are substances capable of counteracting high blood pressure. Examples of such substances include alpha-methyldopa and the pivaloyloxyethyl ester of alpha-methyldopa.

Analgesics are substances capable of preventing, reducing, or relieving pain. Examples of analgesics include morphine sulfate, codeine sulfate, meperidine, and nalorphine.

Anti-pyretics are substances capable of relieving or reducing fever and anti-inflammatory agents are substances capable of counteracting or suppressing inflammation. Examples of such agents include aspirin (salicylic acid),

indomethacin, sodium indomethacin trihydrate, salicylamide, naproxen, colchicine, fenoprofen, sulindac, diflunisal, diclofenac, indoprofen and sodium salicylamide.

Local anesthetics are substances, which have an anesthetic effect in a localized region. Examples of such anesthetics include procaine, lidocain, tetracaine and dibucaine.

Ophthalmics include diagnostic agents such as sodium fluorescein, rose bengal, methacholine, adrenaline, cocaine, and atropine. Ophthalmic surgical additives include alpha-chymotrypsin and hyaluronidase.

Prostaglandins are art recognized and are a class of naturally occurring chemically related, long-chain hydroxy fatty acids, which have a variety of biological effects.

Anti-depressants are substances capable of preventing or relieving depression. Examples of anti-depressants include imipramine, amitriptyline, nortriptyline, protriptyline, desipramine, amoxapine, doxepin, maprotiline, tranylcypromine, phenelzine, and isocarboxazide.

Anti-psychotic substances are substances, which modify psychotic behavior. Examples of such agents include phenothiazines, butyrophenones and thioxanthenes.

Anti-emetics are substances, which prevent or alleviate nausea or vomiting. An example of such a substance includes dramamine.

Imaging agents are agents capable of imaging a desired site, e.g. tumor, *in vivo*. Examples of imaging agents include substances having a label, which is detectable *in vivo*, e.g. antibodies attached to fluorescent labels. The term antibody includes whole antibodies or fragments thereof.

Specific targeting agents include agents capable of delivering a therapeutic agent to a desired site, e.g. tumor, and providing a therapeutic effect. Examples of targeting agents include agents which can carry toxins or other agents which provide beneficial effects. The targeting agent can be an antibody linked to a toxin, e.g. ricin A or an antibody linked to a drug.

Neurotransmitters are substances that are released from a neuron on excitation and travel to either inhibit or excite a target cell. Examples of neurotransmitters include dopamine, serotonin, q-aminobutyric acid, norepinephrine, histamine, acetylcholine, and epinephrine.

Cell response modifiers are chemotactic factors such as platelet-derived growth factor (PDGF). Other chemotactic factors include neutrophil-activating protein, monocyte chemoattractant protein, macrophage-inflammatory protein, platelet factor, platelet basic protein, and melanoma growth stimulating activity; epidermal growth factor, transforming growth factor (alpha), fibroblast growth factor, platelet-derived endothelial cell growth factor, insulin-like growth factor, nerve growth factor, and bone growth/cartilage-inducing factor (alpha and beta), or other bone morphogenetic protein.

Other cell response modifiers are the interleukins, interleukin inhibitors or interleukin receptors, including interleukin 1 through interleukin 10; interferons, including alpha, beta and gamma; hematopoietic factors, including erythropoietin, granulocyte colony stimulating factor, macrophage colony stimulating factor and granulocyte-macrophage colony stimulating factor; tumor necrosis factors, including alpha and beta; transforming growth factors (beta), including beta-1, beta-2, beta-3, inhibin, and activin; and bone morphogenetic proteins.

The aspected particle may be incorporated into a variety of architecture in order to obtain the desired release profiles. Exemplary fabrication methods and drug delivery vehicle architectures include the following.

Aspected particles may be prepared according to conventional methods. For example, the drug and pharmaceutically acceptable excipients may be taken up into solution or may be made into a slurry. The solution or slurry may be cast against a flat surface and allowed to dry into a thin film. The film may be further cut or shredded into aspected particles of the desired dimensions. The films may be formed by air-drying, oven-drying, lyophilization and the like.

In another embodiment of the invention, the drug and pharmaceutically acceptable excipients may be taken up into a liquid to form a paste or dough-like mixture. The mixture may be forced through a screen having the appropriate dimensions. The resulting particles may be dried as described hereinabove. The drug may be incorporated the aspected particles by microgranulation of the drug with suitable pharmaceutically acceptable excipients and then mixing the microgranulars with another bases and coating polymers to form aspected particles and processing the mixture as described herein.

In another embodiment of the invention, the particles may be prepared using a spray drying technique (batch process). A drug solution (1 µg/mL - 5 mg/mL) containing acceptable pharmaceutical excipients may be sprayed on a rotating drum. The drum could be either warm or cooled to subambient. The system could be under reduced pressure (al these parameters are determined by the drug solubility and solvent volatility).

Particle size may be controlled by mechanical milling or cryomilling to reduce the solid mixture to the desired size (1 µm to 7 mm). The preferred range is 1 to 1000 µm, and more preferably 10 - 500 µm. The particles may be used as is or may be fractionated to the desired size distribution using mechanical screens. The desired fractions may be coated with a single or double coating using a Worster Coater. In preferred embodiments, the first coat could be a time release coat while the second coat could provide a slip, a taste masking, a moisture barrier.

Milling of aspected particles may be accomplished using acceptable pharmaceutical processes. Thus, for example, the particles may be compressed between two rollers (when wet) followed by drying to form aspected particles.

In another embodiment of the invention, the aspected particles may be manufactured in a continuous process by spraying a polymeric solution containing the drug and optional excipients onto a moving belt (heated or cooled) to form a thin film, which can be dried and cut into particles. Alternatively, the process may be used to form laminate structures, for example, by first spray coating a film-forming layer, then applying a drug solution to the dried coating layer (in a non-miscible solvent for the coating layer). Thereafter, a final layer may be sprayed on to form a three-laminated product.

The film mono- or multi-laminate sheet may be reduced in size by mechanical mill or cryomill and blended to form uniform aspected particles (1 µm to 10 mm). Further, the aspected particles may be coated as described above to cover edges and/or to add additional desired properties such as to provide a slip, a taste masking or a moisture barrier

In another embodiment of the invention, a liquid may be frozen to form the aspected particle. A cylindrical evaporator with a refrigerant circulation tubing

assembly between its inner and outer surfaces and having an axially driven rotatable shaft in the evaporator center is used. A nozzle on the shaft discharges liquid toward the evaporator inner surface, where it freezes as a sheet, and a blade on the shaft removes the frozen sheet as flakes.

A pharmaceutical preparation may be prepared free of organic solvents for oral administration which contains a meltable active ingredient for a delayed release of the meltable active ingredient and which includes forming a mixture consisting of the meltable active ingredient and a matrix forming auxiliary agent which is meltable and soluble in the active ingredient when the active ingredient is melted; melting the mixture; and kneading the melt until a homogeneous uniform mass is obtained; and forming aspected microparticulates by rolling between rotating drums and mincing the sheet.

The aspected particles of the invention may also be prepared by extruding single or multi-layered thin films 30 incorporating the drug which is then shredded into aspected particles as illustrated in Figure 3A. The multi-layer laminated form contains a core layer 32 in which at least a major portion of the medicament is contained. The core layer consists is flanked by layers 34 containing either water-soluble polymers, water-insoluble polymers, or both, in order to obtain the desired release kinetics. The laminate aspected particle may also contain an outer protective-barrier membrane layer (not shown). Alternatively, the laminate particle may be made up of layers in which each has a difference composition, as shown in Figure 3B. This film is treated is shredded as previously described.

Aspected particles may be formulated as capsules, tablets or powders that may be added to water or other suitable liquid. The particles remain suspended in the liquid so that administration of the drug is accomplished as a drink, avoiding difficulties of swallowing or chewing tablets, or parenteral administration and therefore improving patient compliance. The aspected particles form a fine suspension in water before ingestion, reducing effects of food, presence of bile, and pH, especially on dissolution of sparingly soluble drugs. They prevent absorption in the oral cavity, and allow targeting of drug release at the required absorption site. Drug release can be controlled as described herein to give a therapeutic effect over a any desired time period, e.g., a 24-hour period for a once a day administration.

In the fabrication of fast-dissolving tablets, aspected particles may be incorporated into an effervescent matrix that dissolves in the mouth with or without additional water. The aspected particles then become available and slide easily down to the esophagus. Each aspected particle becomes a sustained release reservoir. Current fast dissolving tablet technologies provide just immediate release and do not provide added benefits as for sustained release capabilities. See, for Example U.S. Patent No. 4,581,232. Alternatively, aspected particles may be formulated into capsules, tablets or powders that could be effervesce on addition of water or form suspensions once added to water (or juice).

In the fabrication of chewable tablets, aspected particles are incorporated into a tablet that could be chewed. Once chewed, the particles become available and slide easily down to the esophagus. Each aspected particle may function as a sustained release reservoir.

In other preferred embodiments, a composition is providing comprising a combination of sustained and rapid release. In one embodiment, aspected particulate formulations may be provided for once-daily oral administration in which the drug is formulated in aspected particle designed to release the drug at a rate such that therapeutically effective blood levels are maintained over 24 hours. The formulation includes a second portion formulated for prompt release to obtain a rapid therapeutic response.

Alternatively, a single particle could be made of a combination of fast and slow release. As an example, an aspected microparticulate comprising: (a) a core of drug or its salt, and an acceptable excipients surrounded by (b) a membrane, containing mostly a water insoluble, film forming synthetic polymers, with a minor amounts of water soluble synthetic polymers; and (c) a final layer of a rapid release form of drug, to provide effective therapeutic amounts immediate after administration.

In another embodiment of the invention an oral formulation for controlled absorption of drugs comprises aspected particulate having (1) a core 40 containing the drug, or its pharmaceutically acceptable salt, and (2) a membrane 42 of at least one film-forming polymer which controls the rate of the drug release into an aqueous medium, as is shown in Figure 4. The aspected microparticulate also could have a

pH-independent dissolution rate.

In another embodiment of the invention, an oral formulation controlled absorption of drugs comprises aspected microparticles having (1) a core 50 of swellable hydrogel that swells in response to stimuli or water, (2) a drug 52 or its pharmaceutically acceptable salt, and (3) a membrane 54 of at least one film-forming polymer which controls the rate of the drug release into an aqueous medium. The swellable hydrogel core will assist to push out the drug payload 56 in a controlled fashioned through the coating, as is illustrated in Figure 5.

In yet another embodiment of the invention, an oral formulation includes a swellable hydrogel, that swells in response to stimuli or water, located in the core of the aspected particle. The core swells in response to stimuli in order to prevent the decrease in the release rate towards the end of the diffusion process of the drug to the environment. The swellable gel core may be used in aspected particles with or without an outer coating used to promote mouth-feel or control drug delivery. It may also be used in aspected particles described above having a membrane of a film-forming polymer which controls the rate of release into an aqueous medium

Once the aspected particles pass the mouth, it may disintegrate in the stomach or gastrointestinal tract to the individual aspected or spherical granulars to increase the distribution over a wide surface area in the gastrointestinal tract. Poorly water-soluble drugs could be incorporated into polymeric films that could be manufactured into aspected particles. For example, polymers such as hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose phthalate, poloxamers or polyethyleneglycols (PEG). The drug could be solubilized or suspended in those polymers. One optional drug state would be of an amorphous state to enhance drug stability and drug solubility. In another method the drug could be crystalline and each crystal is coated separately. Disintegrants could be added to the aspected particle to precisely control the release kinetics. The disintegrants control the water uptake to a hydrophobic matrix and as a result effect the coating of the particle.

The aspected particle could be constructed from multilayers, as shown in Figure 3. Where some layers contain drug and some layers may not contain drugs. The drug will release through the non-drug layers that will act to control the release

barriers. It would also allow the incorporation of a few different drugs into one particle in different layers. In other embodiments, the aspected particle could be constructed by forming an inner, inert core, as shown in Figure 5. Followed by coating the inner core with active pharmaceutical agent. Finally the unit is coated with another layer that could act as taste masking layer and or to control the release layer.

A sustained-release aspected particle includes an excipient or coating; and at least one pH adjuster selected from organic acid, organic acid salt, organic base, inorganic base and base salt. The excipient or coating composition surrounds a core comprising a medicament whose solubility varies with pH. The pH of the excipient or coating composition is adjusted to a desired pH to ensure that the rate of dissolution of the medicament is independent of the pH of the environment in which dissolution occurs.

A time-controlled explosion system in which drug release is caused by explosion of a membrane after a definite time period, said system comprising a preparation in the form of a aspected particles, said preparation comprising a core, a drug, swelling agent and an outer membrane of water-insoluble coating material.

Oral pharmaceutical preparations of aspected particles, which comprise a pharmacologically active drug, bound to small particles of an ion-exchange resin to provide a drug-resin complex having a drug content above a specified value. The drug-resin complex is subsequently coated with a water-permeable diffusion barrier coating that is insoluble in gastrointestinal fluids thereby providing a controllable sustained release of drug under conditions encountered in the gastrointestinal tract.

It is anticipated that the aspected particle may be used in conjunction with a wide variety of drugs. In particular, the aspected particle may be used in the controlled abortion of methyldopa. The aspected particle comprises (a) an aspected particle having a core of methyldopa (or its pharmaceutical salt) and an organic acid; and (b) a membrane or coating surrounding the core mainly comprising a pharmaceutically acceptable, film-forming, water-insoluble polymer. By controlling the number of coating layers permit a controlled release of methyldopa from the pellet. Rate of release over 24 hours after oral administration and is pH independent.

In another embodiment, the aspected particle is adapted to deliver ditiazem. A controlled absorption ditiazem formulation for oral administration includes aspected particles having a core of ditiazem or a its pharmaceutically acceptable salts. A membrane(s) or coating surrounds the core and contains a major amount of a pharmaceutically acceptable film-forming, water-insoluble polymer and a minor amount of a pharmaceutically acceptable film-forming, water-soluble polymer, the number of layers in the membrane and the ratio of the water soluble polymer to water-insoluble polymer being effective to permit release of the ditiazem from the aspected particle at a rate allowing controlled absorption thereof for 12 to 24 hours period following oral administration.

In another embodiment of the invention, an oral deliver vehicle is provided for delivery of verapamil. The formulation includes aspected particles consisting of a core including verapamil and a surrounding membrane or coating consisting mainly of pharmaceutically acceptable, film-forming water-insoluble polymer plus a small amount of a similar water-soluble polymer. The number of layers and the ratio of the water-soluble to water-insoluble polymers in the coating is chosen so that the drub is released at a rate which allows controlled absorption over 24 hr following oral administration, the preferred rate being measured *in vivo* would be T_{max} of 7-10 hr.

The aspected particles may be provided in the form of a gelatin capsule (or similar structure) so that the dosage form could be taken either as a whole or be opened and poured onto food or drink. The packaging may be designed to enhance the ease of opening, a feature particularly attractive to an aging patient population. By way of example, the aspected particles may be provided in a sachet. Thus, a single packaging design of the aspected particles, i.e., a capsule, may be either ingested as an intact capsule or opened and administered as an additive in liguids or other suitable bases.

In yet a further example of the invention, an oral drug delivery vehicle for administering includes a sealable container including a removable seal for holding and storing a desired dose of the pharmaceutically active agent as an aspected particle in a stable condition until needed and a base which is sweetened, flavored and colored to produce a mixture that is palatable and pleasing to the taste. The

1. An oral delivery vehicle, comprising:

an aspected particle including a pharmaceutically active component and excipients, wherein the vehicle is formulated and/or constructed and arranged to provide controlled delivery of the pharmaceutically active component.

2. An oral delivery vehicle, comprising:

an aspected particle including a pharmaceutically active component and excipients, the aspected particle having one dimension that is about an order of magnitude smaller than the other two dimensions.

3. An oral delivery vehicle with an acceptable mouth-feel, comprising:

an aspected particle including a pharmaceutically active component and excipients, the aspected particle having one dimension that is about an order of magnitude smaller than the other two dimensions; and

a lubricious coating on the particle.

4. The delivery vehicle of claim 1, wherein controlled delivery is attained by coating the particle.

5. The delivery vehicle of claim 4, the coating is selected as a diffusion barrier to control drug delivery.

6. The delivery vehicle of claim 4, wherein the coating is selected as a barrier being impermeable to diffusion under a first set of environmental conditions, and permeable to diffusion under a second set of environmental conditions.

7. The delivery vehicle of claim 6, wherein the environmental condition is selected from the group consisting of temperature, pH, ionic strength and particular molecules.

8. The delivery vehicle of claims 1, 2 or 3, further comprising

a base having a consistency capable of being spoon-fed and capable of ingestion

by a patient, the delivery vehicle being disposed therein.

9. The oral delivery vehicle of claim 8, wherein the base may be food or non-food.

10. The oral delivery vehicle of claim 8, further comprising:

a sealable container including a removable seal for holding and storing the aspected particles in a stable condition until needed, wherein the aspected particles and the base are sealed inside the container.

11. The oral deliver vehicle of claim 8, wherein the base is sweetened, flavored and colored to produce a base that is palatable and pleasing to the taste.

12. The delivery vehicle of claim 3, wherein the lubricious coating is a hydrophobic coating.

13. The delivery vehicle of claim 12, wherein the hydrophobic coating is selected from the group consisting of silicone oils, siloxanes and ethyl acetate.

14. The delivery vehicle of claim 3, wherein the coating is a hydrophilic coating.

15. The delivery vehicle of claim 14, wherein the hydrophilic coating is selected from the group consisting of polyvinyl alcohols (PVA), polyvinylpyrrolidone (PVP), polyacrylic acids (PAA), poly(N-vinyl lactams), polyethylene oxides, polyvinyl ethers and derivatives thereof.

16. The delivery vehicle of claim 3, wherein the coating swells to become lubricious in the presence of an aqueous medium.

17. The delivery vehicle of claim 1, further comprising;

a lubricious coating on the outer surface of the aspected particle selected to

mixture and the aspected particles are sealed inside the container. The medication is in a aspected particle form and a delivery medium are stored in a chambered container separated by a rupturable membrane which is ruptured to mix the container contents.

These an other embodiments of the invention are illustrated by way of the examples which are provided for the purpose of illustration only and which are not intended to be limiting of the invention.

Example 1. L-DOPA (Sigma, Lot 55H0565, 1.01 g); sucrose (2.04 g) and purified water (E-Pure, 1.5g) were mixed together. The semisolid mixture was stirred until it became homogeneous and spread on a glass plate and dried at 70 °C overnight. The product was ground to particles of roughly 1 X 1 X 0.1 mm in dimensions. Half of these particles were dipped in 4% solution of ethylcellulose (Benecel) in methyl alcohol (Malinkrodt, Lot 3016KVRG) and air dried.

The aspected particles were placed in phosphate buffer saline solution, pH 7.4 at 37 °C and the solution was analyzed at given time points for the presence of L-DOPA by UV at 287 nm. We obtained an almost linear release of the L-DOPA over 24 hours. There was minimal difference in the release kinetics between the coated and the non-coated aspected particles. In this example the water soluble excipient (sucrose) influenced the release kinetics of the water insoluble drug.

Example 2. L-Dopa (Sigma, Lot 55H0565, 0.2089 g); ethylcellulose (Benecel, Hercules, Lot FP10 13415), 0.3009 g); Avicel (FMC, Lot M723C, 0.4996 g) and purified water (E-Pure) were mixed together. The semisolid mixture was stirred until it became homogeneous and was spread on a glass plate and dried at 70 °C for 4 hours. The product was cut to small square aspected particles of roughly 1 X 1 X 0.1 mm in dimensions. Half of these particles were dipped in 4% solution of ethylcellulose (Benecil) in methyl alcohol (Malinkrodt, Lot 3016KVRG) and dried.

The aspected particles were placed in phosphate buffer saline solution pH 7.4 at 37 °C and were analyzed at given time points for the release of L-DOPA by UV at 287 nm. We obtained a zero order release kinetics for the L-Dopa over 24 hours. The coated particles released 26% of the incorporated L-Dopa while the non-coated particles released 76% of the incorporated L-Dopa over that time period. In this example the water insoluble excipient influenced the release kinetics of the water

insoluble drug and the kinetics was further affected by the coating.

Example 3 Benecel (Hercules, Lot FP10 1345, 0.57 g), Avicel (FMC, Lot M723C, 0.81 g), Magnesium stearate (Malinkrodt, Lot 2256KVKD, 0.13 g) were mixed and purified water (4.9g) was added to form a dough-like mixture. The resulting semi-solid was spread into a screen with 1 X 1 mm opening and placed in a 65 °C oven for 1 h. The dried solid was pushed from the screen to form aspected particles. These particles were divided into three parts: 1/3 of the particles were left as is; 1/3 were coated with a 1.4% Carbopol® solution (poly(acrylic acid), BF Goodrich, Lot CC769F88704) containing 1.4% banana flavor (Frontier); and 1/3 were coated with 1.3% Carbopol solution containing 1% PEG 600 (Union Carbide, Lot IS781428) and 1.4% banana favor. The particles were blind-tasted for their organoleptic feel: the uncoated group felt hard and gritty; the Carbopol coated particles were a bit hard initially and become lubricious; the particles coated with both Carbopol and PEG were lubricious and pleasant tasting from the start. In this example the coating with fast swelling hydrogel improved the organoleptic feel of the aspected particle.

Example 4 Phenylpropanolamine (Sigma, Lot 75F0551, 0.20 g); ethylcellulose (Benecel, Hercules, Lot FP10 13415), 0.30 g); Avicel (FMC, Lot M723C, 0.36 g) and magnesium stearate (Millinckrodt, Lot 2256KVKD, 0.01g) were mixed to form a homogeneous solid mixture. Purified water (E-Pure, 2.1 g) was added and mixed together to form a dough like consistency. The semisolid mixture was spread on a glass slide and freeze dried overnight. The dry product was cut to small square aspected particles of 2 X 2 X 0.1 mm in dimensions. 1/2 of these particles were dipped in 0.3% solution of ethylcellulose (Benecil) in methyl alcohol (Malinkrodt, Lot 3016KVRG) and ½ left as is.

The aspected particles were placed in phosphate buffer saline solution pH 7.4 at 37 °C and were analyzed at given time points for the release of Phenylpropanolamine by UV at 256 nm. In this example the coating retarded the release of a highly water soluble drug phenylpropanolamine.

Particle	$t_{50\%}$	$t_{100\%}$
Uncoated	-	50 min
Coated particles	1 h	8 h

What is claimed is:

enhance mouth-feel.

18. The oral delivery vehicle of claim 1, wherein the controlled drug delivery is attained by selection of appropriate excipients.

19. The oral delivery vehicle of claim 1, wherein the aspected particle is a laminate structure having a core layer comprised of the pharmaceutically active component and outer layers selected to control the delivery of the component from the core layer.

20. The oral delivery vehicle of claim 19, further comprising:
a lubricious coating on the outer surface of the aspected particle selected to enhance mouth-feel.

21. The oral delivery vehicle of claim 1, wherein the aspected particles are incorporated into a tablet, capsule, fast dissolving tablet or chewable tablet.

22. The oral deliver vehicle of claim 1, wherein the aspected particles are incorporated into a capsule configured and arranged to permit opening of the capsule prior to administration to a patient.

Figure 1

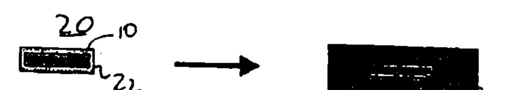

Figure 2

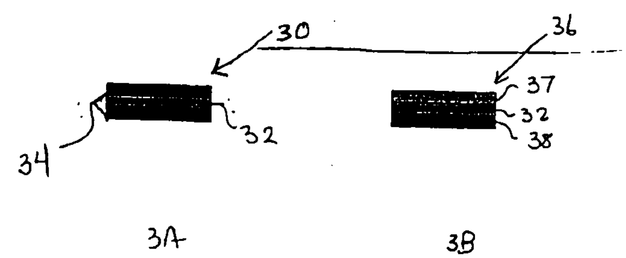

Figure 3.

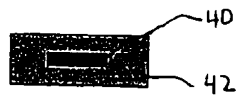

Figure 4

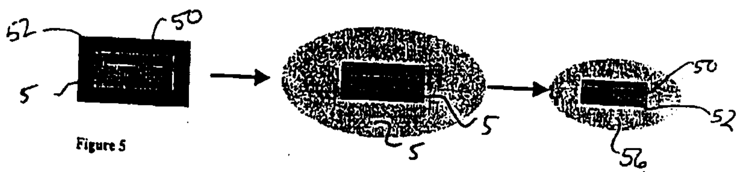

Figure 5

WO8505288

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METHOD AND APPARATUS FOR COATING PARTICLES OR LIQUID DROPLETS

Abstract:

178a Abstract of WO8505288

Solid particles or viscous liquid droplets of core material (27) are encapsulated in a coating material (21) largely as single particles with a single coherent coating, by feeding a suspension of the two materials onto a rotating surface (13). The suspension is centrifugally dispersed by the rotating surface into relative large coated particles (27, 27a) and relatively small droplets (21a) of coating material. Only the size of the droplets of unused coating corresponds to the droplet formed from atomization of the liquid coating material. The size of the coated particles depends on the size of the uncoated particles and is much less dependent upon the atomization characteristics of the rotating surface. Upon being thrown from the rotating surface, or falling from that surface, the droplets (21a) and coated particles (27, 27a) are solidified by exposure to air and are separated by sieving, or the like. The solidified droplets of pure coating material may be recycled into the suspension. Coating of all particles is achieved by dispersing the individual components of core material in the coating material before the resulting suspension reaches the rotating surface.

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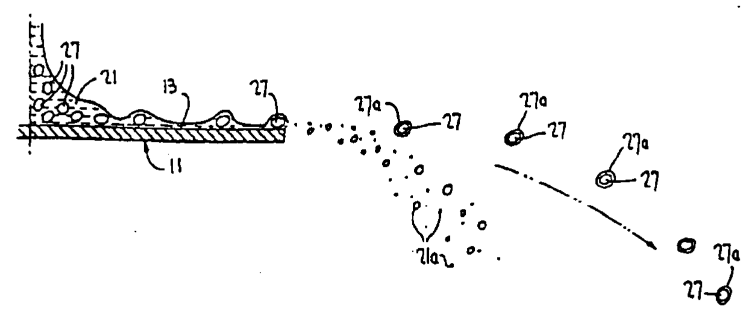

(57) Abstract

Solid particles or viscous liquid droplets of core material (27) are encapsulated in a coating material (21) largely as single particles with a single coherent coating, by feeding a suspension of the two materials onto a rotating surface (13). The suspension is centrifugally dispersed by the rotating surface into relative large coated particles (27, 27a) and relatively small droplets (21a) of coating material. Only the size of the droplets of unused coating corresponds to the droplet formed from atomization of the liquid coating material. The size of the coated particles depends on the size of the uncoated particles and is much less dependent upon the atomization characteristics of the rotating surface. Upon being thrown from the rotating surface, or falling from that surface, the droplets (21a) and coated particles (27, 27a) are solidified by exposure to air and are separated by sieving, or the like. The solidified droplets of pure coating material may be recycled into the suspension. Coating of all particles is achieved by dispersing the individual components of core material in the coating material before the resulting suspension reaches the rotating surface.

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the present invention relates to improvements in such methods and apparatus which provide encapsulation techniques and effects which are unprecendented in the prior art.

2. Discussion of the Prior Art

Coating or microencapsulation of solid particles or liquid droplets is widely employed to protect coated substances from environmental effects and/or control their release time and/or confer improved handling characteristics. Typical products which are coated or microencapsulated are drugs, pesticides, dyes, etc..

Numerous coating or microencapsulation techniques have been employed in the prior art, many of which are described in the Encyclopedia Of Chemical Technology, third edition, volume 15, pages 470-493 (1981), John Wiley and Sons. By and large, these techniques suffer from one or more important disadvantages, including: high cost; inapplicability for coating particles smaller than 200 micrometers in diameter; complexity; long contact time between the core and coating materials prior to solidification of the coating material; inability to achieve wetting and coating of the core particles with the desired coating material; inefficient separation of coated particles from unused coating material and

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inefficient usage or wastage of coating material. Also important in many methods are the tendency for the coated particles to agglomerate and the limited choice of wall materials. There are severe cost disadvantages to most methods because they are batch processes difficult to operate on large commerical scale and because they must employ a solvent for the coating and are unable to use melted coating materials, which require no solvent removal or handling facilities.

There have been a number of attempts in the prior art to provide coating techniques which are devoid of the aforesaid disadvantages. For example, in U.S. patent number 4,386,895 (Sodickson), there is disclosed a rotating apparatus having radially-extending conduits from which hollow needles project radially outward into a reservoir of jelling material. As the apparatus spins, liquid core material is urged by centrifugal force through the conduits and needles. The liquid core material is formed into droplets at the distal ends of the needles, and the droplets are centrifugally thrown into a layer of the gelling material which forms on the outer reservoir wall due to the centrifugal forces produced by rotation. The droplets of liquid core material are thusly encapsulated by the gelling material. This technique works well for its intended

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METHOD AND APPARATUS FOR COATING PARTICLES OR LIQUID DROPLETS

BACKGROUND OF THE INVENTION

1. Technical Field

The present invention relates to a method and apparatus for coating or microencapsulating solid particles or viscous liquid droplets. More particularly,

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purpose. However, it is limited to use with liquid as a core material (i.e., it cannot be used to microencapsulate solid particles) and the minimum size droplet that can be coated depends upon the inner diameter of the needle. As to the latter limitation, there are practical limitations on minimum needle size, particularly when viscous core liquids must flow therethrough.

In U.S. patent number 2,955,956 (Baugh et al.), a rotating disc or table is disposed below a feed pipe through which a slurry composition of coating material is fed. The slurry is spread over the spinning disc surface to form a thin film of the coating material thereon. An annular flow of solid granules is permitted to impinge upon the film on the disc surface, whereupon the granules are coated with the coating material. The coated granules are thrown or are permitted to fall from the rotating disc and are solidified by dry warm gas directed at the falling granules. A second annular flow of granules is directed onto the rotating film to scavenge the unused film and assure that all of it is utilized. Again, this technique is satisfactory for a limited purpose, namely coating granules, such as salt, with additives, but it cannot be readily employed to coat liquid droplets. Moreover, since the granules in the

scavenging outermost annular flow cannot possibly be coated to the same extent as granules in the innermost flow, it is not possible with this technique to achieve uniform coating of all of the granules. Therefore, the Baugh et al. technique is more suitable for wide dispersion of additives onto the surface of granules than it is for coating particles.

British Patent No. 1,090,971 to Wilson, et al., discloses a method of microencapsulating solid particles by forming a dilute suspension of the particles in a dilute solution of a resinous coating material in a volatile liquid, causing the suspension to impinge on a spinning disc whereby the dilute suspension is dispersed as a spray consisting of atomized coating solution and microencapsulated particle droplets, the spray of droplets then being exposed to steam at temperatures above the boiling point of the coating solvent which volatilizes the unwanted liquid solvent so as to leave coated particles plus particles of pure coating of the same size. The process, however, requires a feedstock solution having a very low percentage content of particles to be coated, involves the high temperature removal of a large amount of unused feedstock liquid by volatilization, and does not permit separation by sizing of coated particles from particles of pure coating material.

Objects and Summary of the Invention

It is therefore an object of the present invention to provide an improved method and apparatus for coating or microencapsulating both solid particles and viscous liquid droplets.

It is another object of the invention to provide a method and apparatus for microencapsulating particles which enables at least a majority of the particles to be coated individually or discretely rather than in clusters while simultaneously providing improved means for separating unwanted and unused liquid coating material from the coated particles. More particularly, it is an object of the invention to provide a coating process and apparatus which includes controlled mechanical or physical separation of coated particles from unused liquid coating material by size discrimination, whereby the method is equally applicable to the coating of solid or viscous liquid particles, either with materials including a liquid solvent or with molten coating liquids, and whereby the wettability of the core particles or droplets by the coating material is relatively unimportant, permitting use of the method for a wider variety of core particles and coating materials.

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It is another object of the present invention to provide a method and apparatus for coating or microencapsulating solid particles and viscous liquid droplets over a wide range of particle and droplet sizes, including droplets and particles having diameters well below 200 micrometers.

It is a further object of the present invention to provide a method and apparatus for coating or microencapsulating solid particles or viscous liquid droplets with much less complexity, continuously, at a much faster rate, and at lower cost than is possible in much of the prior art, and to avoid the problem of agglomeration of the particles being coated.

Still another object of the present invention is to provide a method and apparatus for coating or microencapsulating solid particles or viscous liquid droplets wherein coating material can be easily re-cycled back into the process if not used during a first pass through the process.

It is yet another object of the present invention to provide a method and apparatus for coating or microencapsulating solid particles or viscous liquid

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droplets in which coating thickness can be easily adjusted by adjustment of any of plural process parameters.

A further object of the present invention is to provide a method and apparatus for coating or microencapsulating solid particles or viscous liquid droplets wherein the contact time between the core and coating materials prior to solidification of the coating material can be made sufficiently short to prevent degradation of some labile materials, or to prevent their dissolving one in the other when they are partially or totally miscible.

The present invention provides, in a process for coating particles with a liquid coating, a method for obtaining individually coated particles while simultaneously facilitating removal of the coated particles from excess coating liquid with which the particles are mixed in a suspension, the method comprising feeding the suspension onto a rotating surface to separate the suspension into coated particles and atomized liquid droplets expelled circumferentially from the surface, and rotating the surface at a speed yielding a predominance of the droplets of undesired liquid coating of a predetermined size which is smaller than the size of the coated particles.

Thus in accordance with the present invention, solid particles or liquid droplets of core material to be coated are initially dispersed in molten or dissolved coating material to form a suspension. The suspension of the two materials is then fed to the surface of a rotating disc, table or other rotating element. The process parameters, particularly the speed of rotation of the disc or other rotating element are controlled so that the centrifugal forces imposed on the suspension by the disc or the like cause the suspension to spread towards the disc periphery with progressive thinning out of the liquid and separation of excess coating material from the coated particles, with dispersion of the suspension into (1) large coated particles and (2) significantly smaller-size atomized droplets of excess coating material which are formed by atomization of the thin film of liquid coating at the periphery of the disc or the like. Thus, in accordance with the invention, the disc or the like is used as a means for mechanically or physically separating the excess coating liquid from the individually coated particles and dispersing the separated liquid as atomized droplets of significantly smaller size than the coated particles. Most importantly, to obtain the required separation and dispersion, the invention involves relating the rotary speed of the disc to the required size of atomized

droplets of excess liquid coating material to be obtained from the disc, rather than relating the disc speed to the size of coated particles to be obtained. This represents a significant departure from known techniques involving the use of a rotating wheel or the like to provide dispersion of coated particles, where the wheel speed is related to the required size of coated particle products. In practical terms, for coated particles of comparable dimensions, the invention involves rotary disc speeds surprisingly in excess of those used in the prior art techniques.

The average mean size required for the atomized droplets of excess coating liquid may, in practice, be determined by the amount of contamination, i.e., excess unused coating material, which is acceptable in the final product of coated particles, such determination being effected by known techniques involving the relative sizes of the coated particles and the particle size distribution characteristics of unused coating liquid, related to rotational speeds, liquid feed rate, length of wetted periphery, and viscosity in rotary atomizer-type equipment. Typically, in accordance with the invention, the average size of atomized droplets may be about 20% to 75% of the size of the coated particles.

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Since the materials being coated are solid (or viscous liquid), they are not atomized but are simply thrown from the disc as relatively large particles retaining a coating of the liquid in which they were immersed. The control of the process parameters to provide separation of the suspension by the rotary disc into individually coated particles and significantly smaller droplets of excess coating material differentiates the process of the present invention completely from prior art processes such as spray congealing, in which a slurry of dispersed solids is atomized as a liquid, with the product solid present inside the atomized droplets. In spray congealing the dispersed solids are sufficiently finely divided that there are many solid particles in most of the atomized slurry product, and the size distribution of the entire product approximates that predicted from atomization correlations. In spray congealing, when the suspension must behave as a liquid during atomization and no solvent is subsequently removed, the volume fraction of solids in the suspension (and hence, also in the product congealed droplets) has an upper limit near 30%, while in the present invention the volume fraction of coated solids in the product particles may be in excess of 90%, owing to the separation of the unused coating liquid on the rotating disk and its atomization into smaller, easily

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removed particles. In the present invention essentially all of the solids in the feed slurry and all of the coated product solids are larger than the sizes predicted from atomization correlations for the processing conditions employed. An example of the size distribution of the feed solids, product solids and atomized coating obtained is provided in Example VII.

The invention further has clear distinctions from the old art of spray-chilling, in which a suspension is atomized with subsequent solidification of the droplets by cooling, and from spray-drying, in which a solvent is present in the original suspension or solution and is subsequently removed. In both these known processes, the feed suspension or solution is atomized as a liquid, and the products of the processes are the solidified droplets, and there is no separation between particles containing solids and those not containing solids. In principle any atomization device can be used which will give the desired droplets. In the present invention, the process variables are adjusted to give a completely different result, and products can be formed which are impossible to form in general spray-chilling or spray-drying. For example, it is convenient with the process invention to place thin waxy coatings (e.g. 100 micrometers) around solid particles 2 millimeters in

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diameter. In spray-chilling, it would not be possible to pass the feed slurry through a pressure nozzle or two-fluid nozzle, because the core particles would block or plug the orifices in typical nozzles. If a very large nozzle was used to permit the particles to pass, the resultant coarse spray would include many product particles containing no core (just large drops of coating), a few core particles having thin coating, many having thick coating and many in agglomerates rather than as single coated particles. This would occur because particle formation in these orifice devices occurs by atomization of the entire slurry simply as a liquid which happens to contain some solid particles. Such a slurry of large particles could, of course, be passed over a rotating-disc atomizer without any plugging or flow stoppage. However, the disc would be run to treat the slurry as a simple fluid, giving all atomized droplets in the same size range. Again, this means that much of the coating would be in the form of particles as large as the coated particles and many of the particles will be in the form of agglomerates. In none of these cases could most of the unused coating be separated from the coated particles by simple means such as sieving, and the product would contain large inert particles of coating as a major fraction. This is unacceptable in most practical cases.

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By contrast, in the present invention, with a feed slurry containing e.g. 500 micron core particles, and a desired coated product particle of 600 micron average diameter, the disc size, rotational speed, feed rate of the slurry and coating viscosity will be adjusted to force all the unused coating to be in the form of droplets much smaller (e.g. a mean diameter around 250 micrometers) so that most of it can be easily separated from the product, and the product particles will essentially be all in the form of single coated core particles nearly all having an average coating thickness of 50 microns. If it is desired, it is possible to make the unused coating particles smaller, or somewhat larger, while making the desired product.

A key point of the invention is to run the process differently from a typical spray-chilling process. In the latter process, the atomization is set to treat all the feed slurry as a liquid, making droplets in the desired size range. In the process invention, all parameters are adjusted to force all unused particles into a relatively small size, formed by atomization of the film of pure coating, while the large product of coated core particles is thrown off the disc surrounded by the desired amount of remaining liquid, subsequently solidified as a coating.

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The small coating material droplets and the coating-wetted particles resulting from operating the disc in accordance with the invention are thrown or caused to fall from the spinning surface and solidify due to the drying or cooling effect of the surrounding air or gas. Sieving or other size discrimination techniques may be readily employed to remove the coated particles from the much smaller particles of unused coating material and the removal step is facilitated compared with prior art processes because of the size discrimination between the coated particles and the smaller particles of excess coating material which is conferred by the process invention. The coating material particles thusly collected may be re-cycled into the process. The minimum size of the solid particles or liquid droplets which can be coated by this technique is limited only by the size of the particles or droplets themselves and by the lower limit of droplet size of excess coating liquid which can be obtained with a rotating disc (dry particles of 1-5 micrometers at high disc speeds with low viscosity coatings containing solvent). By completely dispersing the particles or droplets in the molten coating material before the materials are placed in contact with the rotating surface, it is possible to coat all particles in a similar fashion. The more uniform the size of the

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dispersed particles the more particle-to-particle uniformity there will be in the coated particles. This has little effect on the size distribution of smaller, atomized excess coating.

Brief Description of the Drawings

These and other objects, features and many of the attendant advantages of the present invention will be better understood upon a reading of the following detailed description considered in connection with the accompanying drawings wherein like parts in each of the several figures are identified by the same reference numerals, and wherein:

Fig. 1 is a diagrammatic illustration of apparatus according to the present invention which may be employed to perform the method of the present invention;

Fig. 2 is a diagrammatic illustration of an alternative embodiment of the present invention;

Fig. 3 is a diagrammatic representation of still another embodiment according to the present invention;

Fig. 4 is a diagrammatic representation of a further embodiment employed in accordance with the present invention;

Fig. 5 is a diagrammatic illustration of yet another embodiment of the present invention;

Fig. 6 is a diagrammatic elevational view of a rotary separating element showing its effect on a liquid suspension when used in accordance with the invention;

Fig. 7 is a diagrammatic plan view of the element shown in Fig. 6;

Fig. 8 is a view similar to Fig. 7 but showing another type of rotary separating element;

Figs. 9, 10 and 11 are diagrammatic views of prior art products (from a spray drying process) including coated particles, the figures representing successive stages in a coating process;

Fig. 12 is a view similar to Fig. 9 showing an intermediate product according to the invention prior to final separation of coated particles from droplets of excess coating liquid; and

Figs. 13 to 15 are diagrammatic views of alternative rotary separating devices useful in performance of the invention.

Description of the Preferred Embodiments

Referring specifically to Fig. 1 of the accompanying drawings, an enclosed spray chamber 10 (with only top wall 12 illustrated in Fig. 1) is provided for performing the method of the present invention. Within chamber 10 there is disposed a rotatable disc or table 11 having an upper surface 13 which may be disposed horizontally. Rotatable disc 11 is rotatably driven about its central vertical axis by means of a variable speed drive motor 17 acting through drive shaft 15. A speed control unit 19 permits adjustment of the rotational speed of the disc 11.

Speed control 19 and motor 17 may be located inside or outside of chamber 10, depending upon the particular application. The disc may be disposed above the motor or suspended below the motor, with appropriate modification of feed lines, supports, etc.

A reservoir 20 is adapted to contain molten or dissolved coating material 21. The reservoir 20 is heated, for example, by means of a heating coil 23 disposed about the reservoir periphery, to maintain the coating material 21 in molten or dissolved form. In this regard, the coating material 21 may be supplied to reservoir 20 in molten form and maintained in that state by means of the heating coil; alternatively, the coating material may be supplied to the reservoir in solid form and melted by the heat derived from heating coil 23. In either case, the molten coating material 21 in the reservoir is in a flowable state. A feed funnel 25 is provided to extend through an opening in chamber 10 so as to deliver individual mass components 27 of core material (e.g., solid particles of core material) to be coated into reservoir 20. In instances where the core material is in the form of droplets of viscous liquid, funnel 25 may be replaced by a droplet-forming tube, a means of feeding an emulsion or the like. A stirrer mechanism extends into the chamber 10 and reservoir 20 and is actuated by a variable speed stirrer motor 30 disposed outside of chamber 20. The stirrer 22, when driven by motor 30, acts to disperse the solid particles 27 (or liquid droplets) of core material throughout the molten coating material 21. The result is a slurry or suspension of the two materials disposed in reservoir

20. This slurry or suspension is delivered through a gravity-feed passage 31, extending from the bottom of reservoir 20, to a ball valve mechanism 33. The ball valve 33 is selectively actuatable from outside chamber 10 by means of actuating rod 35 to control the rate of flow of the suspension material through the ball valve 33. It is noted that the heating coil 23 is disposed so as to heat the suspension as it passes through passage 31 and ball valve 33, thereby assuring that the coating material remains in its molten state while in these components. The outlet passage 37 from ball valve 33 is disposed directly above the axial center of surface 13 so as to deliver the suspension material substantially along the rotation axis of disc 11.

The space above surface 13 is heated, for example, by means of industrial grade heat guns 39, to maintain the temperature on surface 13 sufficiently high so that the coating material in the suspension remains molten. Additional heat is provided at the underside of disc 11, for example, by means of infrared heat lamps 40. Heating may be provided by many methods such as preheated air, steam, radiant energy, induction heating, etc.

The top surface 13 of disc 11 may be smooth or may be provided with a plurality of angularly-spaced radially-extending grooves 24 defined therein, or raised fins, so as to establish paths of travel for the material deposited on surface 13 from ball valve 33. Groovod or vaned surfaces are advantageous if the particles to be coated are small, for example below 200 micometers in diameter, and the coating is viscous, because they can produce finer particles of the unused liquid coating than do smooth discs at the same rotational speed.

In operation, the coating material 21 in liquid or slurry form is disposed in reservoir 20. If the coating material 21 is a wax, the wax is melted by heating. If a polymer coating material is used, it may be dissolved in a solvent, if necessary. The coating liquid may contain emulsified or suspended particles if they are desired in the final wall or coating on the core particle. The core material must be solid particles, granulated aggregates of fine particles or droplets of liquid which is more viscous than the liquid coating material 21. These particles or droplets 27 preferably, but not necessarily, should have a relatively narrow size distribution. When the droplets or particles are fed into the slurry of coating material 21, the stirrer 29 may be actuated by stirrer motor 30 to disperse the particles 27 in the

material 21. With the particles properly dispersed (and this may be a continuous process), the disc drive motor 17 is actuated and set to the desired speed by speed control 19. This desired speed will depend primarily upon the size of the smaller excess coating particles to be produced as described below. Ball valve 33 is then actuated by means of actuator rod 39 to permit the suspension to flow onto the surface 13 of disc 11. Valve 33 is opened slowly until the desired flow rate is achieved. The centrifugal force acting upon the suspension material as it hits the surface 13 causes the material to be thrown radially outward on the surface or grooves 24. This has the effect of dispersing the suspension into both particles 27 wetted with the coating liquid and smaller droplets of coating liquid which do not contain the core particles 27. The heating of the region surrounding disc 11 maintains the coating material in liquid state on surface 13. However, when the material is thrown from or falls from disc 11, the material falls through dry cooler air which causes the coating material to solidify by cooling or drying. The solidified small droplets of excess coating material and the core material coated with the solidified coating material fall to the bottom of the chamber during the

solidification process. Sieving, or other separation techniques, may be employed to separate the coated particles from the smaller particles of pure coating material. The smaller coating material pieces may then be recycled into the process by delivering such pieces into reservoir 20. The majority of the original suspended particles are coated discretely and similarly, a feature which is achieved by virtue of the fact that the original core material particles 27 are carefully dispersed in the coating material before the suspension is fed to the rotating disc. The coating thickness may be varied mainly by changing the viscosity of the coating liquid, but also by adjusting the feed rate of suspension to the disc, by varying the rotational speed of the disc, by varying the diameter of the disc or by varying the number of grooves or vanes.

It is possible to perform the method of the invention as a continuous process by feeding the coating liquid 21 and particles 27 into reservoir 20 on a continuous basis. An endless conveyor belt disposed at the floor of chamber 10 collects the particles and feeds them to a train of sieves which discriminate between coated particles and the smaller particles of pure coating material. The latter may be delivered directly to the reservoir 20 whereas the coated particles may be

dispensed in any manner desired. Alternatively, all of the particles may be pneumatically conveyed into a cyclone, seives or bag filter for separation of smaller excess coating droplets to be recycled.

As previously noted, the process parameters are specifically controlled, in a manner to be described, so as to provide a separation of the liquid suspension by means of the disc into coated particles (generally these will be individually coated particles unless the process is operated at low enough speed so that a small fraction of the particles remain as doublets or triplets, or if there is a wide size distribution of feed particles such that the finer core particles are trapped in larger particles) and droplets of excess coating liquid of significantly smaller size than the coated particles. The effect of the rotating disc on the suspension fed to it is vividly illustrated in Figures 6 to 8. It will be seen that the coating liquid 21 in the suspension is gradually pulled away from the core particles 27, forming a liquid film on the disc, as the suspension moves from the center toward the periphery of the disc, with progressive decrease in thickness of the liquid film or sheet and finally separation of the excess liquid from the particles 27, leaving a coating layer 27a on the particles and dispersing the excess coating into a spray

of small droplets 21a formed from the thin coating film. Figures 6 and 7 show this effect for a disc with a smooth upper surface, and Figure 8 shows the effect with a grooved disc. The size of the atomized droplets of excess coating bears little relation to the size of the solid coated particles, but depends rather on the film spreading and atomization characteristics of the liquid coating alone. The core particles, by contrast, move by a totally different mechanism, not spreading into a film but simply being thrown through or along the film of coating, issuing from the disc periphery with a small amount of associated coating material.

Figure 12 shows a typical product in accordance with the invention as it is sprayed or expelled from a rotating surface. It will be evident that the product consists of core particles 27 with a liquid coating layer 27a all generally of similar size, and droplets 21a of excess unused coating material 21 which are of significantly smaller size than the coated particles and which have a size distribution typical of that expected for simple atomization of the pure coating liquid. The product shown in Figure 12 is in vivid contrast to typical products of prior art processes which use a rotary wheel or the like to provide dispersion of

suspended particles. Thus, Figures 9 to 11 show the product of a typical prior art process (spray drying) in which particles are imbedded in droplets of a liquid containing a solvent, by forming a slurry of the particles in the liquid and forming droplets of the slurry by feeding the slurry to a rotary wheel or the like. As shown in Figure 9, the product as it leaves the wheel contains particles 127 with a liquid coating 127a and separated droplets 121 of excess coating material. However, it will be evident that there is no sharp size discrimination, as in products of the present invention, between the coated particles (which are usually coated in clusters, but some of which will be coated singly) and the droplets of excess coating material. Thus, there are a significant number of droplets 121 which are comparable in size to the coated particles, in contrast to products of the present invention where the droplets predominantly are significantly smaller than the coated particles and most large particles are coated discretely. Accordingly, subsequent removal of excess droplets of coating material, by sieving, centrifuging or the like, is facilitated with products according to the invention compared with the products of the prior art processes. Figure 10 shows the prior art product of Figure 9 after evaporation of the solvent, and Figure 11 shows the product after removal of the smaller excess coating

droplets, for example by sieving, illustrating the rather high percentage of unused coating material (in the larger droplets thereof) which has not been removed from the coated product. It is essentially impossible by this prior art process to produce product particles with core loadings above 50%, to remove excess coating, and to have high particle-to-particle uniformity. Looked at in the alternative, the invention provides a product comprising relatively large, predominantly individually coated particles and uncoated droplets predominantly of significantly smaller size than the coated particles, whereas prior art products are predominantly a mixture of individual mass components of coated particles and uncoated droplets of generally similar dimensions wherein the core particles themselves are relatively small compared to the final particles.

In order to obtain a product wherein there is a sharp size discrimination between the coated particles and the droplets of excess coating liquid, the process parameters in accordance with the invention are controlled in a particular manner. More particularly, in accordance with the invention, the rotational speed of the disc or the like is related to the average mean size required for the droplets 21a (as will be described in more detail below) rather than relating the rotational

speed of the disc or the like to the average size required for the coated particles. By contrast, in the prior art processes, the speed of the rotary wheel or the like is related to the size required for the formed droplets irrespective of whether they contain imbedded core particles or not. Thus, in the present invention, the disc or the like is run at surprisingly higher speeds than in the prior art for producing coated core particles of similar size to the particles of the prior art.

As noted above, in carrying out the invention, the speed of rotation for the disc is related to the required mean droplet size for the excess coating material rather than to the required size of coated particles and in this process, changes in the disc speed have significantly less effect on the thickness of coating on the large core particles. It is well known in industrial spray drying and spray chilling techniques using rotary disc-type atomizers that there are mathematical correlations between the disc speed and the average droplet size expelled from the disc, see for example pages 179-184 of "Spray Drying Handbook" by K. Masters, 3rd Edition, John Wiley & Sons, New York (1979), and which is specifically incorporated herein by reference. These correlations may be used to provide an estimate of required disc speed for the present invention, (possibly incorporating a

viscosity correction factor in the correlations to compensate for the effect of hot air flow as in Figures 3 and 4) once the desired average droplet size for the excess coating liquid has been established. This desired average droplet size may be established from known droplet size distribution estimates, for example, using log-probability graphs (also discussed in the above reference) and relating the estimated droplet size distribution to the acceptable contamination percentage in the final product, i.e., the percentage of acceptable excess coating droplets of a size making them impractical to separate from the coated particles. Again, it should be stressed that while techniques are known for estimating disc speed in relation to a required droplet size and for estimating droplet size distributions, these have not previously been utilized in the present manner whereby, in a particle coating process, disc speed is related to a predetermined size required for the droplets of excess coating liquid rather than being related to the size required for the coated product particles themselves. Also, it is understood that the correlations referred to above for determining the required disc speed may be used for estimation purposes, and in practice, it may be desirable somewhat to adjust the disc speed empirically.

To illustrate the significant difference in rotational speeds used in processes according to the invention compared with prior art processes, the various parameters used in a typical prior art spray cooling-type particle embedding process may be compared with the parameters used in a process in accordance with the invention for coating like particles with a like liquid coating. Thus, for example, if it is required to coat ion-exchange resin beads having a sieve fraction 53-106 microns with a wall material of 9/1 paraffin wax/Elvax 420 (Dupont ethylene-vinyl acetate copolymer, melt index 150) in a spray cooling procedure in accordance with a typical prior art process, the rotational speed of an 8-inch diameter (0.2 meter) disc type atomizer typically would be set at about 3,000 r.p.m. for a feed rate of 4.5 kg/hr of slurry containing 2/1 wt ratio of coating to core particles, with a coating viscosity of 50 centipoise to give an average fluid drop in the atomized slurry close to the size just containing the largest core particle. For the largest single core particle at 70% loading in the final microcapsule, this droplet size would be 120 microns and setting the rotational speed at 3,000 r.p.m. would give an average droplet size of about 118 microns from the correlation noted above. However, this will be the average particle size in the atomized slurry both for particles containing the core material

and also for droplets of the excess pure coating material. A product obtained from this prior art process at these conditions showed a substantial overlap in particle size distribution of the coated particles and the unused coating droplets so that it was not practical to effect a separation based on size.

By contrast, in a process in accordance with the present invention, if it is estimated that the smallest microencapsulated product including the above beads will have a diameter of 67 microns at approximately 50% loading of the 53-micron core particle, the rotational speed of a disc may be set for example to run at 8,000 r.p.m. to give an average particle diameter for unused coating droplets of about 40 microns. To estimate the amount of unused coating droplets which might be in the microencapsulated product, a log-probability graph, as described above may be used and results in a contamination rate of about 10% for a product sieved at 67 microns. A run was also made under these conditions, but using an 8-inch vaned disc giving somewhat smaller droplets of excess coating. After sieving at 53 microns, the contamination, measured by counting coated particles and remaining pure coating particles, was approximately 7%.

The correlation referred to above with the viscosity term modified to mirror the effect of hot air moving over the surface is:

$$\bar{x} = \frac{(1.4 \times 10^4)(M_L)^{0.24}}{(Nd)^{0.83}\,(\pi d)^{0.12}}\left(\frac{V}{15}\right)^{0.1}$$

where $\bar{x}$ = Average droplet diameter (microns)
M_L = Liquid feed rate (kg/hr)
N = Rotational speed (RPM)
d = Disk diameter (meters)
V = Viscosity (centipoise)
πd = Wetted periphery (meters). Use nh for disks with n vanes or grooves h meters high.

As noted above, one of the parameters which may be adjusted to vary the thickness of the coating material on the final coated particle is the viscosity of the coating liquid. In this regard, when wax is employed as a coating material, the viscosity can be readily lowered

to thereby provide thinner coating walls on the final coated particle, by adding solvents to the molten coating material 21. When the inclusion of a polymeric material, e.g., polyethylene in the coating is desirable the viscosity can be lowered significantly through addition of compatible materials of substantially lower viscosity, e.g., waxes. In general, the solid particles 27 of core material should be insoluble in the liquid coating material 21; however, if the contact time between the core material 27 and the coating material 21 is sufficiently short before the coating material solidifies, solids may be coated before they dissolve. In this way, water soluble or water sensitive solids may be coated by an aqueous solution. Likewise, droplets of viscous liquids (i.e., of significantly greater viscosity than the coating material 21) may also be coated.

In some applications the materials may be selected such that the solid core material 27 reacts with the coating liquid 21 so as to form an initial solid wall at their juncture before the coating material 21 is solidified during the process. Thus, the core material 27 might contain a polyfunctional acid chloride, or isocyanate, and the liquid 21 might contain a polyamine or polyol. This technique is also useful for coating a liquid since the initial wall or shell formed by the

chemical reaction between the two materials prevents absorption or dispersal of the core material into the coating material or aggregation of the core particles before the coating material solidifies.

Coatings of slurries may be formulated by suspending the solids desired in the coating liquid prior to, or simultaneously with, the suspension of the core particles. Suspended solids in the coating may be soluble in the coating if their contact time with the coating is insufficient to permit dissolution.

Liquids may also be coated by dispersing them to form a suspension or emulsion in the coating liquid. The core liquid should have a viscosity higher than that of the coating liquid so that the spread of liquid and subsequent atomization into small drops occurs primarily in the coating liquid. Liquid core materials may also be coated after they are absorbed onto or into solids.

It is also possible to catch the coated particles on a layer of powder or in a hardening or extraction bath in which additional solvent is removed by extraction or in which a chemical hardening reaction occurs. An example of the latter would be the formation of

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gelatin-coated particles which are caught in a bath containing glutaraldehyde which hardens the wall or coating material and greatly decreases the permeability of the wall.

It is possible to use the invention to produce walls of polymers which are insoluble in all or nearly all solvents when the polymers are available in the form of aqueous latex suspensions. Examples are acrylics, rubber, synthetic rubber, polyvinylidene chloride, etc. The solid or droplet core particles are suspended in the latex and the suspension fed to the rotating element according to the present invention. Moist air must be blown over the disc surface or other means provided to prevent the latex from drying and coagulating on the disc. After the coated particles and smaller excess pure latex particles leave the disc they are dried, e.g., by falling through a chamber through which hot unsaturated air or gas is passing. As water is removed from the latex, the polymer particles coagulate into an insoluble film. When dry the film coating is a tight barrier only affected by solvents for the polymer.

Another embodiment of the present invention is illustrated in Fig. 2 to which reference is now made. A rotating disc 11 with a grooved top surface 13 and its

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drive motor 17 are similar to like components illustrated in the embodiment of the Fig. 1. Infrared heat lamps 40 are employed to heat the space above disc 11 and a stirrer motor 30, having its speed controlled by a VARIAC 41, stirs the coating and core materials to provide the necessary suspension. A heated funnel 45 is selectively raised and lowered along three threaded vertical support rods 49, only two of the support rods being illustrated in Fig. 2. The stirrer 50 is disposed within funnel 45 and is rotated by means of drive shaft 47 connected to stirrer motor 30. The distal end of shaft 47 is in the form of a plug 51 which, depending upon the height of the funnel 45 on support rods 49, may project through the lower funnel opening and thereby close off outflow from the funnel to the disc 11. This embodiment eliminates the ball valve and provides flow control by means of the raising and lowering of the funnel on shafts 49, or by raising and lowering the motor. Many more feed schemes will be apparent to those skilled in the art.

Another embodiment of the present invention is illustrated in Fig. 3 to which detailed reference is now made. A rotating disc 55 having a smooth flat upper surface 57 is disposed horizontally between two horizontal walls 59 and 60. A funnel 61 contains a stirrer 63 placed to suspend solid particles in liquid

coating material which is added simultaneously to the stirred funnel. The lower end of funnel 61 extends through a suitably provided opening 65 in upper wall 59 so that the bottom opening of funnel 61 is disposed to permit the funnel contents to fall on the disc surface 57 in alignment with the rotation axis of the disc. A distribution cone 67 diverges downwardly and is disposed substantially concentrically about the funnel stem so as to prevent splashing of the slurry material delivered from the funnel to the disc surface. Hot air is channelled to the region between plates 59 and 60, both above the disc 55 and below it, by means of suitable hot air conduits 69 which communicate with suitable openings in plates 59 and 60. The temperature of the air delivered through conduits 69 is sufficient to maintain the coating material in molten form when it is located in the region between plates 59 and 60. It is apparent that the plates aiding in controlling air flow need not be parallel. For example, higher hot air velocity at the edge of the rotating disc can be achieved with the gap between plate and rotating disc decreasing as the radius increases. It is also apparent that the plates may rotate in common with the disc.

In the Embodiment of Fig. 3, the funnel 61 serves as the vessel in which the solid particles or liquid droplets of core material are dispersed in the coating

liquid. In addition, the feed rate of the resulting suspension from the funnel onto disc surface 57 is controlled by the level of suspension maintained in the funnel rather than by a funnel outlet valve mechanism.

The embodiment of Fig. 4 is similar in many respects to the embodiment of Fig. 3 except for the suspension feeding mechanism and for the fact that the disc is tilted at an angle, e.g., forty-five degrees, relative to horizontal. The suspension of coating and core materials is disposed in a vessel 70 having a stirrer 71 therein. A lower corner portion of the vessel 70 is selectively openable to permit controlled feeding of the suspension material onto the top surface 57 of disc 55. Fig. 4 is intended to illustrate that the disc can be oriented at substantially any desired angle and need not be horizontal as shown in Figs. 1 - 3.

The embodiment of Fig. 5 diagrammatically illustrates the use of a generally conical mesh screen 77 disposed above the top surface of a disc 75 so as to converge to a location between the disc and the lower end of a funnel 73. The funnel delivers the suspension material toward the disc 75 in the manner described above in relation to the embodiments of Figs. 1 - 3. However, the mesh screen 77, which rotates with disc 75, is

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provided to aid in controlling the average coating thickness by draining away part of the coating material through the screen. Further forms of rotary discs 90, 92, 94 which may be used for the invention are shown in Figs. 13 to 15. In addition, multi-tier rotating discs, vaned wheels, grooved discs and radial tubes can be employed.

The invention as described hereinabove is suitable for coating particles of substantially any shape; however, the most uniform coating is obtained with spherical particles. Particle size may generally vary in the range from 10 micrometers to 10 millimeters, although special designs or conditions will permit the use of particles outside this range. Nearly spherical particles may be readily formed by techniques well known in the prior art, such as spray drying or prilling, by extrusion or compression in molds, or by agglomeration of fine powders in rotating drums using a liquid phase binder and/or heat. It is also known that compact crystals approaching a spherical shape may be obtained by attrition during crystalization.

The preferred coating material for minimum process cost should be liquid at coating temperature and should solidify when cooled, without requiring either

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evaporation of a solvent or a chemical reaction. The viscosity of the coating material may range from 0.5 to 100,000 centipoises, with preferred viscosities between 1-5,000 centipoises. Preferred coating liquids are various mixtures of polyolefins, ethylene-vinyl acetate copolymer and waxes. A typical coating liquid composition is 50 percent by weight polyethylene of density 0.92, melt index 250, and 50 percent paraffin wax having a melting point of 60° C. It is preferable that the core material is insoluble in the coating liquid at coating temperature, although soluble cores can be coated if the contact time with the coating before spraying and solidification is sufficiently short to prevent dissolution.

During a typical operation, as noted above, the particles to be coated may constitute up to 45 percent by volume of the overall suspension slurry, although in general the percent by volume will be in the 20-35% range. The temperature surrounding the top surface of the disc must be above the melting point of the coating material. Typically, this may be between 60° and 90° C for pure waxes and 120° to 160° C for polymer/wax mixtures.

The rotational speed of the disc is chosen so that the excess coating material produces much smaller spheres than the coated particles. If the disc were used simply as an atomizer for the coating liquid it is these small spheres which would be produced. Since the excess liquid wall material forms smaller droplets, the aerodynamic drag force per unit mass is much higher than that for the larger coated particles. Hence, as these smaller droplets solidify they are slowed down much more quickly by the drag force as they move away from the spinning disc. These droplets, therefore, fall much closer to the spinning disc. A receiver may be placed near the disc to catch these small unused coating particles for recycling back to the coating reservoir. Alternatively, the unused coating particles may be caught in the inner portion of the bottom cone for sieving and recycling.

When the ring of unused coating particles partly overlaps the ring of coated particles, the particles cannot be totally separated by sieving. When this occurs, an increase in rotational speed of the disc causes a separation of the rings, by throwing the coated particles farther and decreasing the size of the unused coating particles so that they fall closer to the disc. When the product particles are less than 100 microns in diameter, both the product and the smaller excess coating

particles fall within a few feet of the disc and are both strongly affected by the air blowing outward along the radius of the disc. Hence they do not separate cleanly into distinct rings. However, they are easily separated by sieving, centrifugal force, etc.

For particles in the range of 0.5 millimeter diameter and a density of 1.2, a rotational speed of 1,000 - 1,500 rpm for a disc of 8 inches diameter provides good spatial separation of the fine excess wax particles from the much larger coated particles so that the excess wax particles may be collected separately and may not require a separate sieving operation.

The particles to be coated may be mixed with the melted coating material immediately before the resulting suspension is fed to the disc. Feeding rates for a disc having an 8 inch diameter are preferably on the order of 100 milliliters to 5 liters per minute but can cover the range of 10ml/min to 100 liters/min. For coating materials with melting points substantially above room temperature (e.g., above 50° C), the coated particles solidify rapidly after leaving the disc surface and may be collected immediately. If a solution is used as the coating, then the solvent has to be evaporated before essentially dry particles can be collected.

The embodiments described above include a disc having a grooved surface, a disc having a flat smooth surface, cupped or cone-shaped surface, and angled screens or perforated plates disposed above a reservoir (rotating or non-rotating). It is also possible to provide a vaned disc whereby the disc comprises a plurality of angularly spaced vanes with gaps therebetween. Virtually any rotating device which can be used for atomization may be used in the present application, as long as the slurry does not have to pass through a fine orifice where plugging may occur.

Other alternatives are an inverted cone made from stainless steel screen and a vaned disc in which the vanes are placed at an angle to the disc diameter.

In employing the invention, we have successfully coated the following substances: phosphors (12-60 micrometers), potassium chloride angular particles (25-300 micrometers), potassium chloride (approximately spherical particles 500-860, 250-500, 120-250 micrometers), water thickened with carboxymethyl cellulose, sucrose crystals (1-1.5 millimeters), sucrose spheres (1.4-2 millimeters), aspirin powder (held together with carboxymethyl cellulose solution),

acetaminophen (180-320 micrometer spheres), etc.. Coating liquids which we have employed include pure wax, wax with solvents (e.g., paraffin wax 20 percent, Polywax 500 30 percent, 1,1,2, trichloroethane 50 percent), wax mixtures (Polywax 500 16 percent, ethylene vinylacetate copolymer (Elvax 420, 18% vinyl acetate, Du Pont de Nemours, Inc.) 24 percent and paraffin wax 60 percent; or paraffin wax 17 percent, Polywax 500 33 percent and Elvax 420 50 percent), polyethylene wax, wax and low density polyethylene (paraffin 50 percent and polyethylene 50 percent), Woods metal (50 percent Bismuth, 25 percent Lead, 12.5 percent Cadmium and 12. 5 percent Tin), cellulosic polymer dissolved in a solvent, and solutions of mixtures of waxes, polyethylene and ethylene-vinyl acetate copolymer in aromatic and aliphatic hydrocarbons. Coating materials have also been used in the form of slurries containing up to 37 mass percent of suspended insoluble solids, both smaller than and greater than the average final wall thickness.

The present invention is further illustrated by the following examples:

EXAMPLE I

In this example, nearly spherical particles of potassium chloride were used, the particles being of a 20-32 mesh (500-863 micrometers) fraction obtained by sieving. The apparatus was substantially that illustrated in Fig. 1 with the top surface of disc 11 smooth rather than grooved. The outlet opening 37 for the ball valve was disposed approximately 1/8 inch above the surface 13 of the disc. The entire reservoir was heated by electrical tape and was equipped with a thermocouple. The disc was inclined at about 45 degrees from horizontal (as in the Fig. 4 embodiment) to increase the path of the upward-directed particles in the air so as to allow them to solidify before encountering a solid surface. (The downward-directed particles were not collected). The disc assembly was equipped with three heat guns above the disc and two below the disc in addition to the two heat lamps.

Thirty-eight grams of paraffin wax (Fisher P-22), 38 grams of Polywax-500 (made by the Bareco Division of Petrolite Inc.), and 24 grams of Elvax 420 (DuPont) were melted and mixed in a beaker. The molten wax and 38 grams of potassium chloride particles were mixed in the heated mixing reservoir. With all the heat guns on, the

disc was then turned on to rotate at 700 rpm. The valve was opened to allow the suspension to flow onto the center of the disc from which it was dispersed. Coated potassium chloride was thrown in an upward trajectory (because of the angle of the disc with respect to horizontal) landing at floor level roughly six feet away from the disc. The smaller pure wax particles followed a path much closer to the disc, separated by one or two feet from the coated potassium chloride particles.

The large particles were separated into three fractions by sieving. Twenty-eight percent were greater than 860 micrometers in diameter; 68% were between 590 and 860 micrometers in diameter; and 4% were less than 590 micrometers in diameter. The small wax particles immediately around the disc were not recovered.

The mean diameter measured for a small number of uncoated particles (n=15) was 521 $\pm$ 44 micrometers. The coated particles had a mean diameter of 759 plus or minus 74 micrometers (N = 15). Therefore, the mean wall thickness based on these measurements was 119 micrometers.

In the fraction having a diameter greater than 860 micrometers, all the particles sank in a liquid of density approximately 10% greater than that of the wax

(i.e., diethyl succinate having a density of 1.047 grams per cubic centimeter). This indicates that all these particles contained potassium chloride. In the particles having diameters in the range of 590-860 micrometers, three particles out of twenty randomly chosen particles floated, indicating that they were pure wax. (The fraction of pure wax particles in this size range could be decreased by higher disc speed or lower coating viscosity). Water extraction showed that the fraction having diameters greater than 860 micrometers contained 54.7% potassium chloride, and 45.3% wax; the fraction having 590-860 micrometer diameter contained 65% potassium chloride and 35% wax.

Whereas the free potassium chloride dissolved within seconds when placed in water, less than 3% of the coated potassium chloride (of either size fraction) dissolved in ten minutes. Only 16.2% dissolved in 70 minutes from the 590-860 micrometer fraction, and 30.9% dissolved in 70 minutes from the fraction having diameters greater than 860 micrometers. In 266 minutes, 39% dissolved from the fraction in the range of 590-860 micrometer diameter, and 62% from the fraction having diameters in the range greater than 860 micrometers. This indicates that the soluble potassium chloride particles were well coated.

In this example (I) the potassium chloride was well coated by the waxy polymer coating. This is difficult by methods such as fluid-bed coating because the waxy droplets do not wet the potassium chloride surface well. Hence, the coating spreads poorly over the surface. In the present invention, the particles start by being totally immersed in the coating, and the process is so rapid that the coating does not have sufficient time to uncover the surface before solidifying.

EXAMPLE II

Non-pareil sugar spheres ranging from 1.2 to 2 millimeters in diameter were encapsulated in wax having the following composition: Gulfwax (household paraffin wax) 38 grams; Polywax 500 (Bareco) 38 grams; and Elvax 420 (DuPont) 24 grams. While the wax was stirred at 104° C in the mixing vessel, 40 grams of non-pareil spheres were added, mixed well and the dispersion was poured on to the disc, which was spinning at 1140 rpm. The resulting wax coating on the coated non-pareils ranged from 17 to 25% by weight when measured by extraction. Uncoated non-pareil spheres released 73.6% of their contents in ten minutes and 91% in thirty minutes.

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Coated spheres did not release a detectable amount in ten minutes (i.e., less than 1%). After thirty minutes, 1.1% was released, and after one hour 2.6% was released. Hence, the sugar was well coated.

EXAMPLE III

Twenty grams of cellulose acetate butyrate (Eastman CAB 381-2) were dissolved in a mixture of 100 milliliters dichloromethane and 10 milliliters acetone and placed in reservoir 20. Red sugar crystals having a total weight of 28 grams and passing through a 500-micron sieve but retained by a 250-micron sieve were mixed with the CAB solution and the suspension fed to the disc rotating at 1170 rpm without heating. The red particles were well separated from the smaller, uncolored polymer droplets during the coating operation. The fraction of the coated product passing a 1 millimeter sieve but retained by 860 micrometer openings (coated particles agglomerated on the receiving surface due to inability to evaporate all the solvent in the laboratory air) were 68% sugar and 32% cellulose acetate butyrate coating. When placed in water, 33% of the sugar dissolved in ten minutes, and 65% in 90 minutes.

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EXAMPLE IV

In order to coat with polymeric compositions of higher melt viscosity (e.g., polyethylene), it is necessary to control the air temperature adjacent to the rotating disc. This was achieved to a greater extent using the embodiments of Figs. 3 and 4 wherein the cover plates 59 and 60 were employed. Hot air (for example, from heat guns) is conducted directly through conduits 59 toward the disc.

100 grams of polyethylene (melt index = 250) was melted in a beaker. 34 grams of spherical granules of slightly water-soluble organic acid, having a number mean diameter of 0.740 millimeters, was mixed with the molten polyethylene. The temperature of the mixture was 154° C. This was delivered to the disc which was rotating at 1140 rpm. The temperature of the plates facing the disc ranged from 130° to 170° C at different points. The viscous suspension was fed to the plate over a period of five minutes. 46 grams of material which did not contact a wall were recovered and were distributed as follows:

Diameter (Micrometers)	% of total	Content
500	7.8	Polyethylene only
500-590	0.9	Polyethylene only
590-860	7.3	coated organic acid
860-1000	14.5	coated organic acid
1000-1180	9.1	coated organic acid
1180 particulate	3.7	several spheres
non particulate	56.7	"taffy" and "spider webs", polyethylene containing no organic acid.

(The non-particulate material is not observed at lower coating viscosity, but higher temperature could not be employed in this example to lower the viscosity owing to the thermal instability of the core particles).

For comparison, the particle size distribution of the uncoated organic acid spheres was as follows:

Diameter (micrometers)	wt %
500	0.4
500-590	1.2
500-860	79.2
860-1000	19.0
1000	0.3

The particles in size fraction 590 to 1000 micrometers contained 49% organic acid. When placed in deionized water 2.4% of the organic acid was released in 16 hours, 7.1% in 72 hours. In the uncoated control runs, the organic acid dissolved entirely in approximately 30 minutes.

EXAMPLE V

400 gm Woods metal, (obtained from Federated Metal Corp. of Newark, N.J.) was melted in a beaker. 50 gm of nearly spherical KCl, passing a sieve with 860 micron openings but being retained by a 500 micron sieve, was heated to 85° C in an oven. An 8-inch disc with twenty-four grooves 1/8 inch wide and 1/16 inch deep, held at 60° C and an inclination of 28 degrees with the horizontal, was rotated at 6,300 rpm. A suspension of KCl particles in the liquid Woods metal was formed and poured onto the disc.

The distribution of particle sizes was as follows:

Diameter (micrometers)	Wt/(gm)	Content
Below 500	26.3	metal dust
500-590	21.8	spheres
500-860	10.0	spheres and flat pieces
Above 860	37.1	agglomerates

The spheres were covered with the metal as determined by visual observation, but the potassium chloride dissolved readily, indicating that the coating was porous. Under the microscope the coating was seen to consist of many small metal crystals, giving the likelihood of leakage at crystal boundaries.

EXAMPLE VI

50 gm Polyethylene USI (density = 0. 927, melt index = 250) was dissolved in 50 gm Gulfwax Paraffin at 150°C. The flat, smooth 8-inch diameter disc was held at 130°C

and rotated at 1,800 rpm. 50 gm of nearly spherical acetaminophen particles, 177 - 250 micrometers was mixed with the polymer/wax solution. The 177 - 300 micrometers product fraction contained mostly coated single particles.

EXAMPLE VII

The cone-screen embodiment of Fig. 5 was employed in coating nearly spherical KCl. The percent core material relative to total particle (i.e., payload) increased in the product from a run made under the same conditions using a flat disc. This demonstrates that the porous cone represents another means to control wall thickness by increasing the amount of coating liquid drained away from the core particles, and also decreases the fraction of excess coating liquid atomized from the edge of the rotating device. There is, however, a decrease in the number of discretely coated particles.

Coating composition was 38% by weight paraffin wax (Gulf), 38% by weight Polywax 500, Bareco, and 24% Elvax 420 (Dupont). Original particle size range was 0.50 to

86 mm. The slurry was fed to the disc or rotor at 116 degrees centigrade, with the air between the plates kept at 129-133'C.

	% Payload	
	500-590 micrometers	590-850 micrometers
Flat Disk	75.8	57.3
Cone Screen	88	82.8

For the smooth disc, operated at the same conditions the size distributions of uncoated core particles, coated particles and atomized excess coating were as follows:

Uncoated KCL

Diameter (micrometers)	Weight (gm)	%
Smaller than 420	.418	2.5
420-500	2.354	14.0
500-590	13.187	78.6
590-860	0.654	3.9
Larger than 860	0.172	1.0
Total	16.785	100.0

Product (in two rings around rotating device):

Coated KCL Particles (Outer Ring)

Diameter (micrometers)	Weight (gm)	%
Smaller than 500	.3	1.8
500-590	.6	3.6
590-860	12.1	73.4
860-1.00	2.6	15.8
1.00-1.18	0.5	3.0
Greater than 1.18	0.4	2.4
Total	16.5	100.00

Atomized Excess Coating (Inner Ring)

Diameter (micrometers)	Weight (gm)	%
Smaller than 149	1.0	5.5
149-177	0.9	5.0
177-250	1.5	8.3
250-297	3.3	18.3
297-420	7.3	40.6
420-500	1.3	7.2
Greater than 500	2.7	15.1
	18.0	100.00

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There is only a small overlap in the size distribution of the large coated KCL particles (mostly single coated particles) and the small droplets, which consist mostly of atomized pure coating material. Since solid KCL is more dense, nearly all coated KCL particles would be in the outer circle. If the disc is operated at higher rotational speed or if the viscosity of the coating is decreased, the diameter of the atomized droplets in the inner ring decreases. The diameter of the ring containing the large coated particles will increase if rotational speed is increased, or will decrease slightly if speed is kept the same but viscosity is decreased, because they have a thinner coating.

We have described an improved method and apparatus for coating or microencapsulating solid particles or viscous liquid droplets applicable to a wide range of sizes. The coating technique works well for coating solids in the 20-300 micrometer range where prior art methods of spraying the coating onto fluidized particles work poorly or not at all. In general the method is less expensive than prior art processes because it is very rapid and requires less energy and process control. Contact time between the coating material and the core material can be maintained extremely short. In addition, the particles need only be handled once in the apparatus as opposed to many passages through the spray region of the spray coating methods.

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The present invention is also useful in place of a variety of other processes for forming microcapsules. For example, the method of the present invention obviates the need for careful control and timed changes in conditions required in many cases of coacervation and solvent evaporation microencapsulation processes. The present method avoids the difficulties of microcapsule agglomeration, a frequent problem in these processes.

The method of the present invention is also useful with dispersed liquid core droplets, made more viscous than the coating liquid to limit the spreading and atomization phenomena to the less viscous coating material. In this manner, the process of the present invention may be employed to form microcapsules similar to those formed by the annular-jet method.

Having described several embodiments of the new and improved method and apparatus for coating or microencapsulating solid particles or viscous liquid droplets in accordance with the present invention, it is believed that other modifications, variations and changes will be suggested to those skilled in the art in view of

the foregoing description. It is therefore to be understood that all such variations, modifications and changes are believed to fall within the scope of the invention as defined in the appended claims.

WHAT IS CLAIMED IS:

Claim 1. A method of coating or encapsulating individual mass components of core material having the form of solid particles, aggregates formed by granulation or liquid droplets with a coating of material that is less viscous than the core material and solid at normal room temperatures but liquid at elevated coating temperatures, or in the form of a solution during the coating process, said method comprising the steps of:

distributing said individual mass components of core material throughout the liquid coating material to form a suspension;

feeding the suspension onto a rotating surface which centrifugally separates and disperses the suspension into (1) droplets of pure coating material and (2) individual components of said core material coated with said coating material;

cooling the coated individual mass components or removing solvent therefrom to solidify the coating material;

and controlling the process so as to produce a predominance of the droplets of excess liquid coating as droplets of a predetermined size smaller than the size of the coated individual mass components.

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Claim 2. The method according to Claim 1 wherein the step of controlling the process includes relating the speed of rotation of the surface to said predetermined size of the droplets.

Claim 3. The method according to Claim 1 further comprising the step of separating said coated individual mass components from the droplets of pure coating material.

Claim 4. The method according to Claim 3 wherein the step of separating includes sieving or use of centrifugal force to separate the relatively large coated individual mass components from the relatively small droplets of coating material.

Claim 5. The method according to claim 3 wherein the step of separating includes rotating said rotating surface at sufficiently high speed such that the droplets of pure coating material are significantly smaller than the coated individual mass components and therefore fall from said rotating surface at a location radially inward from the separated coated individual mass components.

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Claim 6. The method according to Claim 1 wherein the step of cooling or removing solvent includes passing the coated mass components through ambient air or gas, heated or unheated, by centrifugally hurling the components from said rotating surface.

Claim 7. The method according to Claim 1 further comprising the step of heating the region at said rotating surface to maintain the coating material in liquid form at said rotating surface.

Claim 8. The method according to Claim 7 wherein the step of heating includes passing hot air between a plate or plates positioned a short distance above and below said rotating surface, or heating said plate or plates by induction.

Claim 9. The method according to Claim 1 wherein the step of distributing comprises the steps of:

heating said coated material in a vessel to sufficiently high temperature to maintain the coating material in liquid form;

dispersing said individual mass components of core material into said coating material in said vessel; and

stirring the contents of said vessel to form said suspension of individual mass components distributed throughout said coating material.

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Claim 10. The method according to Claim 1 wherein the rotating surface is oriented at an acute angle relative to horizontal.

Claim 11. The method according to Claim 1 further comprising the step of adjusting the thickness of the coating material on said core material by adjusting the rotational speed of said surface.

Claim 12. The method according to Claim 1 further comprising the step of adjusting the thickness of the coating material on said core material by adjusting the viscosity of the liquid coating.

Claim 13. The method according to Claim 1 further comprising the step of adjusting the thickness of the coating material on said core material by adjusting the rate at which said suspension is fed onto said rotating surface in said step of feeding.

Claim 14. The method according to Claim 1 further comprising the step of adjusting the thickness of the coating material on said core material by adjusting the wetted surface of the rotating device.

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Claim 15. The method according to Claim 1 further comprising the steps of:

draining a portion of said coating material, which is fed as part of said suspension to said rotating surface, by providing porosity in said rotating surface as with a mesh cover or porous material or perforated material disposed in the form of a cone or bowl in spaced relation above a further receiving surface;

centrifugally dispersing the coated mass components, which are larger than the interstices or perforations of said mesh cover, along said mesh cover while partially draining the liquid coating material, by gravity, such on and/or centrifugal force, away from the coated mass components as the mass components move along the mesh cover; and

passing said liquid coating through the mesh cover and recycling the passed liquid coating material.

Claim 16. The method according to Claim 1 further comprising the steps of:

solidifying said droplets of coating liquid by centrifugally projecting them from said rotating surface through ambient air or gas (heated or unheated, depending on whether the coating is a melt or a solution);

collecting the solidified droplets of coating material; and

recycling the collected droplets of coating material.

Claim 17. The method according to Claim 1 further comprising the steps of:

solidifying said droplets of coating material; and

recycling the solidified droplets of coating material by returning them to said suspension.

Claim 18. The method according to Claim 1 further comprising the step of adding a solvent for said coating material to dissolve the coating material prior to or during the formation of the suspension to permit coating or to reduce the thickness of the coating material on said coated mass components.

Claim 19. The method according to Claim 1 wherein said core material is insoluble in said coating material.

Claim 20. The method according to Claim 1 wherein said core material is at least partially soluble in said coating material, and wherein the time from initial contact between said core and coating materials to solidifying of said coating material is sufficiently short to prevent significant dissolution of said core material into said coating material.

Claim 21. The method according to Claim 1 wherein the core material or a component contained thereon reacts with the coating material or a component contained therein to form an initial solid wall at the periphery of each individual mass component before said coating material solidifies.

Claim 22. The method according to Claim 1 wherein said core material is in the form of liquid droplets having a higher viscosity than that of the coating material.

Claim 23. The method according to Claim 1 further comprising the step of hardening the coated mass components by transferring them to a chemical hardening bath.

Claim 24. The method according to Claim 23 wherein said coating material is a gelatin and said hardening bath includes glutaraldehyde.

Claim 25. The method according to claim 23 wherein the coating is gelatin and hot gas, air or non-solvent liquid is contacted with the gelatin to cause cross-linking and insolubilization.

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Claim 26. The method according to Claim 22 wherein said individual mass components are generally spherical particles having diameters in the range of 10 micrometers to 10 millimeters.

Claim 27. The method of claim 1 wherein the coating liquid is a suspension containing fine insoluble particles which become part of the coating on the core particles, and are equally as well distributed in the excess coating liquid.

Claim 28. The method according to Claim 1 wherein said suspension is flung radially outward along said disc surface in radially-extending angularly-spaced grooves formed in said surface.

Claim 29. In a process for coating particles with a liquid coating, a method for obtaining individually coated particles while simultaneously facilitating removal of the coated particles from excess coating liquid with which the particles are mixed in a suspension, the method comprising feeding the suspension to a rotating surface to separate the suspension into coated particles and atomized liquid droplets expelled circumferentially from the surface, and rotating the

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surface at a speed for obtaining a predominance of the excess pure coating droplets of a predetermined size which is smaller than the size of the coated particles.

Claim 30. The invention of Claim 29 wherein the volume percentage of particles to be coated in the suspension is in the range 10-35%, preferably 20-35%.

Claim 31. The invention of claim 29 wherein coated particles of temperature-labile material (chemicals, enzymes, biological cells) are formed with simultaneous formation of smaller droplets of excess coating material, so rapidly that little or no degradation or denaturation occurs.

Claim 32. The invention of claim 29 wherein the core mass components to be coated are poorly wetted by the coating liquid (wetting angle less than 90°) but are completely coated by virtue of having been completely immersed while in suspension and having the process of liquid spreading and particle radial passage and solidification occur too rapidly for the uncovering of the core to occur.

Claim 33. A product comprising (a) individual mass components of core material having the form of solid particles, aggregates formed by granulation, or liquid droplets coated or encapsulated in a liquid core material, and (b) droplets of pure liquid coating material of significantly smaller size than the coated mass components, the product being produced by the process as claimed in claim 1.

Claim 34. Apparatus for coating or encapsulating individual mass components of core material having the form of solid particles, aggregates formed by granulation, or liquid droplets with a coating of material that is less viscous than the core material and solid at normal room temperatures but liquid at elevated coating temperatures, or in the form of a solution during the coating process, said apparatus comprising container means for containing the individual mass components of core material and the liquid coating material in the form of a suspension, feed means for feeding the suspension from the container means onto a rotating surface for centrifugally separating and dispersing the suspension into (1) droplets of pure coating material and (2) individual components of said core material coated with said coating material, cooling means for cooling the coated individual mass components or for removing solvent

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therefrom to solidify the coating material, and means for controlling the apparatus to produce a predominance of the droplets of excess liquid coating as droplets of a predetermined size smaller than the size of the coated individual mass components.

Claim 35. The invention of claim 34 wherein the controlling means includes means for relating the speed of rotation of the surface to the predetermined size of the droplets.

Claim 36. The invention of claim 34 including means for separating the coated individual mass components from the droplets of pure coating material.

Claim 37. The invention of claim 34 including heating means for heating a region at said rotating surface for maintaining the coating material in liquid form at the rotating surface.

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FIG. 1

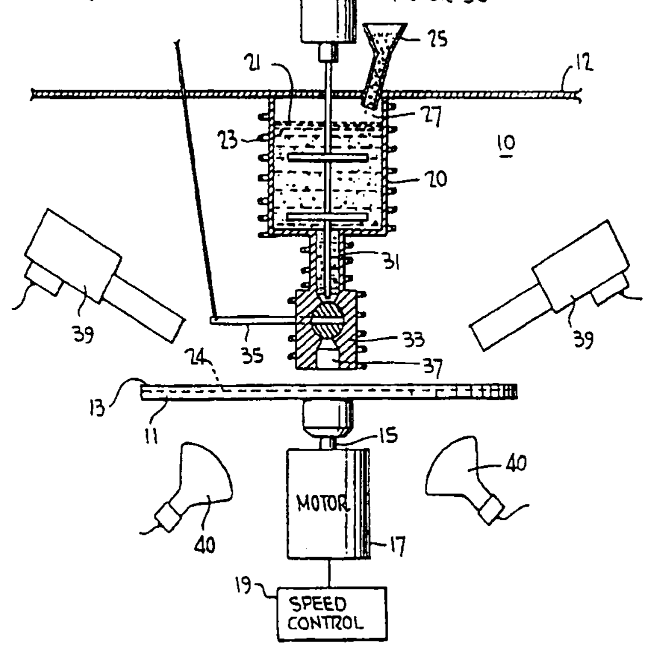

FIG. 2

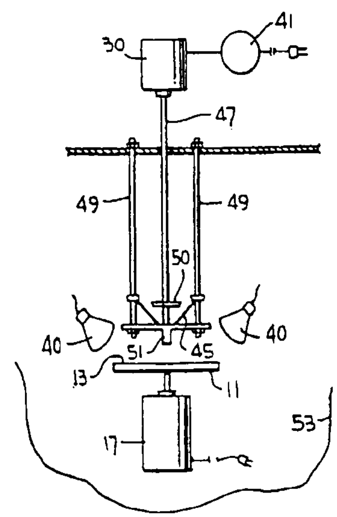

FIG. 5

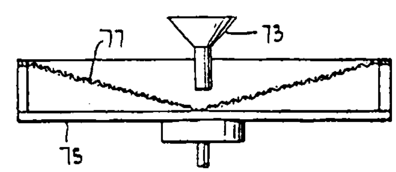

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FIG. 3

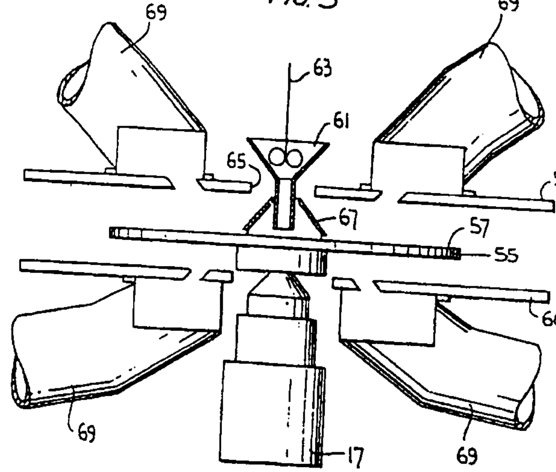

FIG. 4

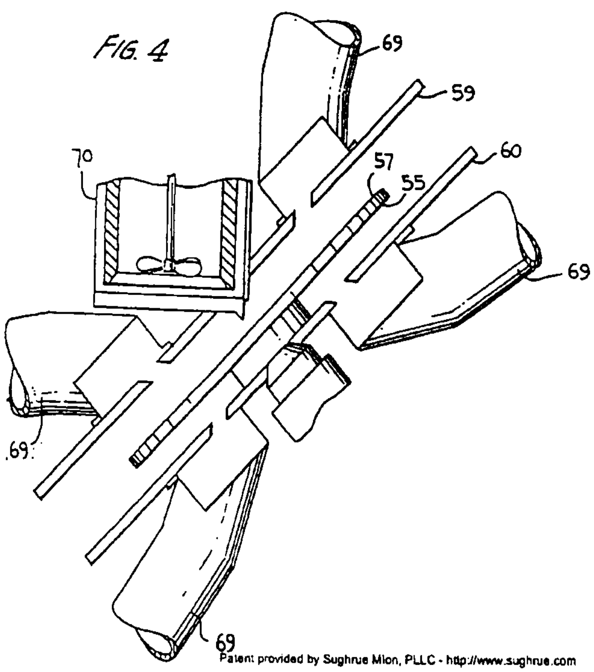

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FIG. 6

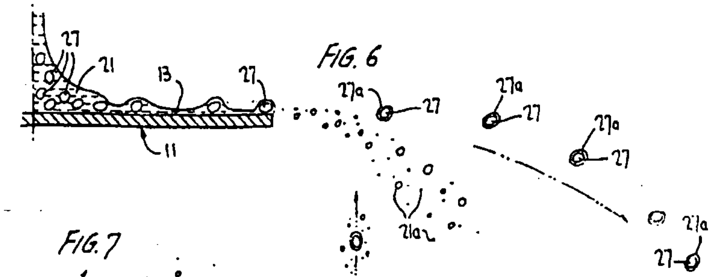


FIG. 7

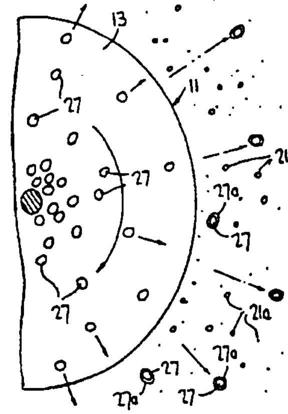


FIG. 8

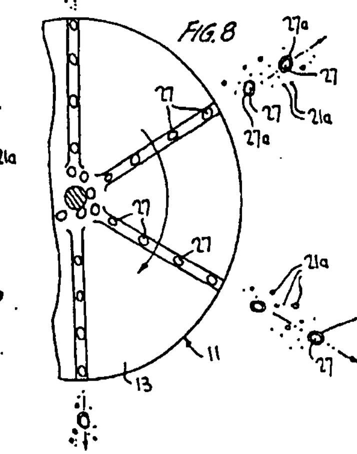


FIG 9 (PRIOR ART)

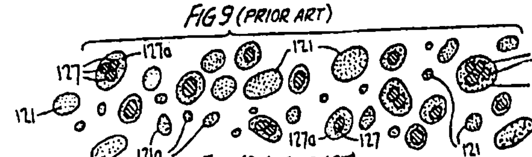


FIG. 10 (PRIOR ART)

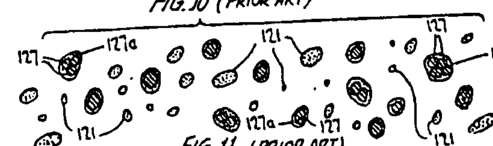


FIG. 11 (PRIOR ART)

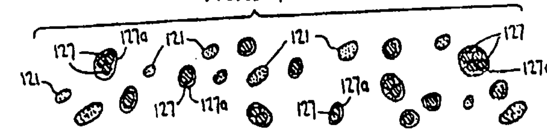


FIG. 12

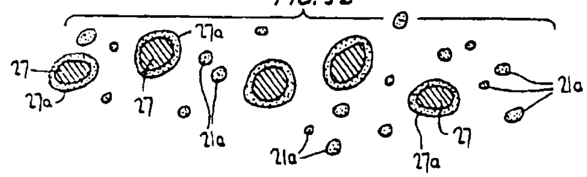


FIG. 13

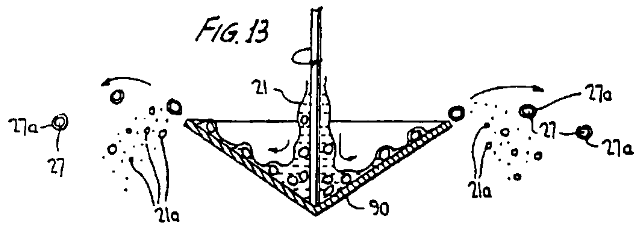


FIG. 14

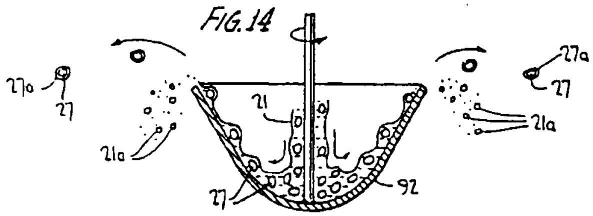
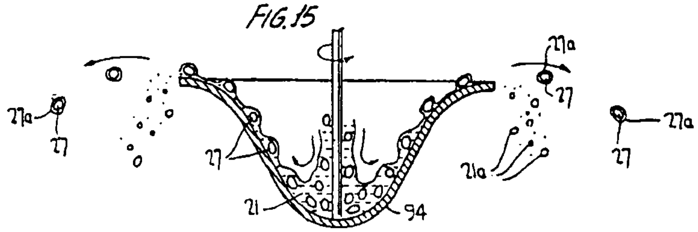


FIG. 15



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INTERNATIONAL SEARCH REPORT

International Application No PCT/US 85/00827

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC^4: B 01 J 13/02; A 61 J 3/07

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
IPC^4	B 01 J A 61 J

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [6]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	US, A, 4123206 (CLARENCE C. DANNELLY) 31 October 1978, see column 3, lines 14-68; column 4, lines 1-43; figure 1 --	1,2,3,4,5,6, 10,11,16,17, 29,33,34,36
A	US, A, 4386895 (LESTER A. SODICKSON) 7 January 1983, see column 3, lines 33-68 (cited in the application) --	1,2,19,23, 26,28,29,34, 35
A	US, A, 2955956 (CHARLES BAUGH et al.) 11 October 1960, see column 3, lines 39-69 (cited in the application) --	1,6,8,16,19, 34
A	GB, A, 873757 (VITAMINS LTD) 26 July 1961, see page 2, lines 68-130; page 3, lines 1-20 --	1,2,6,24
A	Derwent, volume 75, nr. 1, 4 February 1975, Section C.:"Agricultural Chemistry", Derwent Publication Ltd. (London, GB) & JP, B, 49049294 (CHISSO CORP.) 26 December 1974, see abstract --	1,15

* Special categories of cited documents: [10]

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
26th August 1985	27 SEP 1985
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	G.L.M. Kruydenberg

Form PCT/ISA/210 (second sheet) (January 1985)

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International Application No. PCT/US 85/00827

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	DE, B, 1185109 (VITAMINS LTD.) 7 January 1985 see column 7, lines 10-65; figure 2	1,7,9,34
	--	
A	FR, A, 1433421 (DUNLOP RUBBER CO.) 21 February 1966 & GB, A, 1090971 see page 1, left-hand column, paragraph 2 page 6, left-hand column, paragraph 3 (cited in the application)	1

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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/US 85/00827 (SA 9599)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 17/09/85

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 4123206	31/10/78	US-A- 4218409	19/08/80
US-A- 4386895	07/06/83	None	
US-A- 2955956		None	
GB-A- 873757		None	
DE-B- 1185109		None	
FR-A- 1433421		GB-A- 1090971	

For more details about this annex :
see Official Journal of the European Patent Office, No. 12/82

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